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# ARCHIVES OF DISEASE IN CHILDHOOD.

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# A SYNDROME IN THE RAT RESEMBLING PINK DISEASE IN MAN

BY

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(From the Laboratories of the Imperial Cancer Research Fund and the National Hospital, Queen Square, London.)

Of the diseases which have come into prominence since the War none is of more interest or importance than the condition first described in Australia by Swift<sup>11</sup> as occurring in infants and young children, and now known as Swift's disease, erythroedema polyneuritis, or more colloquially as 'pink disease.' The syndrome was recognised in America by Weston<sup>14</sup> and in this country by Thursfield and Paterson<sup>12</sup>. Cases have since been recorded from France, Holland, Switzerland and Sweden. As Paterson and Greenfield<sup>9</sup> point out, the disease appears to have become commoner during the past few years, some hundreds of cases having now been recorded. The ætiology of the condition is unknown.

The object of the present paper is to point out the close resemblance between the clinical symptoms and pathological findings in Swift's disease and those which occur in a disease of the rat possibly caused by absence from the diet of a vitamin-like factor distinct from the vitamins at present recognised. For the sake of brevity the disease in the rat will be referred to as the 'pink disease,' but without prejudice.

## 'PINK DISEASE' IN YOUNG RATS.

The clinical symptoms of this syndrome in the rat were first described by Boas<sup>2</sup> who produced the condition in young rats by feeding them on a complete diet except that the sole source of protein was supplied by fresh, crude egg-white which had been dried. The clinical symptoms as described by Boas are as follows:—For the first two or three weeks the young rats grow well and are usually in good health. Then red scaly patches appear at the corners of the mouth, the coat becomes rough and sticky and the long hairs fall out. The fur on the abdomen shows at first a characteristic ribbed appearance, followed by the development of bald areas. Meanwhile the red patches spread to other parts of the body and the picture is one of an eczematous dermatitis. There are even skin hæmorrhages in severe cases. The region round the mouth is always the most severely affected, though there is often such severe blepharitis that the eyes are closed. The loss of hair is often extensive. In a few cases œdema of the feet occurs. The rats always have a distinctive, somewhat musty, smell. The body weight remains stationary for a week or two, but falls slowly during the second stage of the disease. This is reached two or three weeks after the development of the first signs of deficiency. To the dermatitis symptoms of nervous upset are now added. There is pronounced spasticity of the limbs, particularly of the hind legs, and the back is arched. The rat assumes in many cases a kangaroo-like posture. Some of the rats do not show marked spasticity but assume a crouching attitude and display a curious swimming movement with the front paws. Death, which occurs

in the final phase, is preceded by a rapid loss of weight and the animal shows signs of extreme cyanosis. Rigor mortis sets in rapidly. Post mortem there is an almost complete absence of fat, and the skin is infiltrated and vascularised, but these are the only apparent abnormalities, the organs seeming perfectly normal. No extensive histological study was carried out, but sections of liver, kidney, thyroid, spleen and adrenals failed to show any marked change.

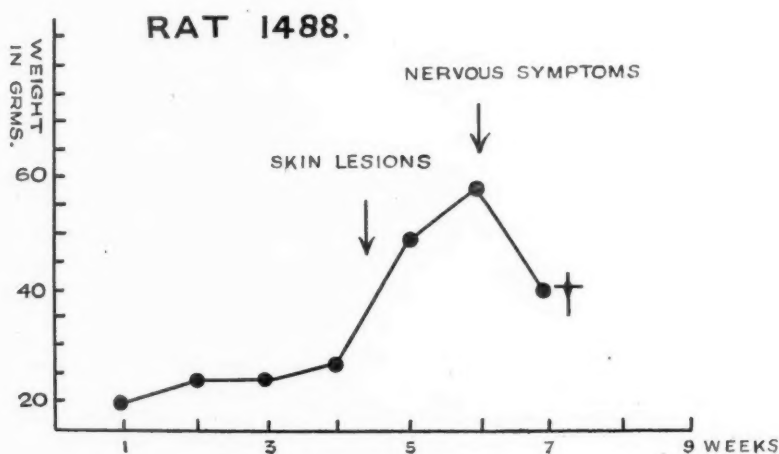
During histological investigations of the changes in rats due to lack of vitamin B<sub>2</sub> which have been described elsewhere (Findlay<sup>6</sup>), attention was drawn to the syndrome described by Boas and an attempt was made to repeat her observations.

Young rats bred from laboratory stock were, when 20-30 gm. in weight placed on the following diet:—

Dried egg-white ... ..	100 gm.	Cotton seed oil ... ..	75 gm.
Wheaten starch ... ..	250 ..	Lemon juice ... ..	25 c.cm.
Salt mixture (McCollum,		Marmite ... ..	25 gm.
Simmonds and Pitz <sup>8</sup> ) ...	25 ..	Distilled water ... ..	300 c.cm.

Each rat received 5 drops of cod-liver oil daily. This diet thus contains an ample supply of vitamins A, B<sub>1</sub>, B<sub>2</sub>, C and D. Its content of vitamin E is, however, low. The weight curve of a typical rat fed on this diet is shown in Chart I, together with the time of onset of the cutaneous and nervous symptoms. The terminal loss of weight would seem to be correlated with the extreme muscular weakness which prevents the animal from feeding properly. Before the onset of the nervous symptoms the animal feeds well and there is no loss of appetite such as occurs in deficiencies of the antineuritic vitamin. There is little to add to the description of the clinical symptoms as given by Boas. The temperature remains normal throughout except during the terminal

CHART I.



phase of inanition when it becomes subnormal. The earliest skin lesions are usually seen around the mouth, on the lower jaws and front of the neck. At a later stage when the skin lesions are fully developed and fissured, the rats tend to keep their mouths constantly open, due possibly to the irritation of the skin lesions or to weakness in the muscles of the lower jaw. Blepharitis is a very constant symptom but keratomalacia never developed. The earliest nervous symptoms consist in a slight straddling of the hind legs. Later the characteristic gait develops. When the animal wishes to move forward the back is arched to the kangaroo position. Then slowly one hind leg is raised until the foot is from a half to three quarters of an inch from the ground; still very slowly the foot is lowered and the process is repeated with the other hind leg. The gait is thus more reminiscent of an ataxic than of a spastic type of paralysis. After lasting for from two to three days this stage is followed by one of intense muscular weakness. If the animal is placed on its side it can right itself only with the greatest difficulty, if at all.

Blood examinations were made from the tail veins of a number of rats. The average leucocyte count for normal rats of the same weight was 8,750 per c.mm.; for the deficiently fed rats 10,600 per c.mm. Differential leucocyte counts did not show any significant variation, while the number of red blood corpuscles varied only within normal limits.

*Pathological Observations.* Apart from the skin lesions, the most conspicuous changes at death were the disappearance of the subcutaneous and peritoneal fat, and the wasted condition of the muscles, more especially those of the hind legs. The spleen and thymus also showed atrophy, while the adrenals were slightly enlarged. In rats killed before the onset of the nervous symptoms, however, the changes due to inanition were absent. Death, in the majority of cases, appears to be due to inability to take food as, post-mortem, the stomach is usually empty. Broncho-pneumonia was present in a small number of animals. The papillomatous condition of the cardiac portion of the stomach which is common in rats fed on diets deficient in vitamins A and B<sub>2</sub>, was also not infrequently seen.

*Histological Changes.* Zenker's fluid and formol saline solution were used for the fixation of the internal organs, followed by staining with Weigert's hæmatoxylin and van Gieson. Boveri's solution was also used for fixing the skin, while for the adrenals, Cramer's osmic vapour method was employed for the demonstration of adrenalin.

In a typical rat dying in the terminal stages the histological appearances were as follows: No significant changes were noted in the liver, kidneys or pancreas. In the alimentary tract the papillomatous condition of the cardiac portion of the stomach was not infrequently encountered, while in the intestine both the muscular walls and lymphoid structures had undergone atrophic changes. In the spleen and thymus there was a reduction in the number of lymphoid cells. Broncho-pneumonic changes were sometimes seen in the lungs. The pancreas, thyroid, and genital organs did not show any deviation from the normal. In the bone marrow certain rats showed signs of early

gelatinous degeneration. Sections of the muscles of the hind legs showed a general thinning of the muscle-fibres which had shrunk to two-thirds or less of their normal size, with the result that the sarcolemma nuclei appeared more prominent and more numerous than in the normal muscle. The intermuscular connective tissue septa stood out very clearly with an increase in the cellular elements. In some cases the intramuscular nerve branches also showed a slight excess of cell nuclei.

*Skin.* The cutaneous lesions were very similar to those described by Denton<sup>5</sup> in black tongue in dogs, and by Findlay<sup>6</sup> in rats fed on diets deficient in vitamin B<sub>2</sub>. The earliest changes were congestion in all the small vessels of the cutis vera, with œdema of the surrounding tissues. Later, there was a proliferation of the reticulo-endothelial tissue around the vessels and hair follicles, the nuclei being increased and deeply stained. There was no polymorphonuclear exudate round the hair follicles, except when ulceration and an invasion of saprophytic micro-organisms had occurred. The cells of the hair follicles appeared shrunken and atrophic. The cells of the epidermis were not hyperplastic, but the whole process of keratinisation was very active, there being an excessive scaly desquamation of the horny layer. In some places where desquamation had occurred the epidermal cells were reduced to a single layer. Similar changes to those described in the skin, though in less degree, were seen in the epithelium forming the mucous membrane of the mouth.

*Nervous System.* The brain and spinal cord of each rat were fixed in formol saline, together with one sciatic nerve, whilst the other was fixed in Muller's fluid. Sections were taken from the cervical, dorsal and lumbar regions of the spinal cords. The following staining methods were used:—on frozen sections toluidin blue and Scharlach R; on celloidin sections toluidin blue and hæmatoxylin with van Gieson counter-stain. Nerves fixed in formol saline were teased and used for the study of  $\pi$  granules with toluidin blue staining after mordanting with Muller's fluid. Marchi preparations of the nerves fixed by Muller's fluid were made and embedded in celloidin.

The outstanding lesion was that in the spinal cord. Here there was diffuse infiltration with small round cells, greater in the grey matter, but apparent also in the white matter and extending in most cases throughout the length of the cord. This finding was practically constant, being completely absent only in two rats. The infiltration varied somewhat both in amount and extent, but where it did not involve the entire cord the dorsal and lumbo-sacral region appeared to be most affected. With the toluidin blue stain, the small round cells stained an intense blue which did not allow of any differentiation of the chromatin. With iron hæmatoxylin they stained very deeply, but appeared to be slightly granular. In some rats the infiltrating cells were distinctly larger and stained less deeply, their appearance resembling that of small neuroglial cells. A few sections from the spinal cords of these rats were stained with Anderson's Victoria blue stain for neuroglia, but this failed to reveal any excess of neuroglial fibres. The infiltration occurred diffusely; it was not limited to white or grey matter, but it was certainly most obvious in the region of the

posterior horns. In several cords it was possible to see the infiltration extending into the posterior nerve roots but unfortunately it is difficult to be certain about the condition of the anterior nerve roots as most of these had been torn off in the process of preparation of the sections. In one or two sections, however, in which the anterior nerve roots were still present, no infiltration could be seen in them.

Most cords were greatly congested and there seemed to be an excessive number of capillaries present. No perivascular infiltration, however, could be determined.

The nerve cells in the anterior horns were relatively healthy. In a few, early vacuolation could be seen, but nowhere could we find the intense vacuolation and swelling which was so pronounced a feature in the cords of rats fed on a diet deficient in vitamin B<sub>2</sub> (Stern and Findlay<sup>10</sup>). A few cells also had pale-staining Nissl granules, but there was no evidence anywhere of acute chromatolytic changes.

In Scharlach R. preparations there was no trace of lipochrome pigment in the nerve cells, neither could we demonstrate any products of myelin destruction.

The changes in the peripheral nerves were slight but definite. In most sciatic nerves early degeneration could be seen by the Marchi method. Minute droplets of black-staining lipoid were found lying along the course of the nerve fibres. These droplets were most obvious at the nodes of Ranvier. In two rats the brachial plexus was stained by the Marchi method. Neither of these nerves showed any evidence of degeneration. Preparations of peripheral nerves which were stained for  $\pi$  granules were negative. Only a very few granules could be found, not more than were present in the nerve of a normal rat.

The brains appeared perfectly normal, no infiltration with cells being found above the cervical region of the cord.

#### 'PINK DISEASE' IN BREAST-FED RATS.

Boas<sup>2</sup> in attempting to explain the action of dried egg-white in giving rise to the clinical syndrome described above, suggested that the phenomena observed might be explained by one of the following hypotheses:—

(1) When fresh crude egg-white is dried an essential dietetic factor in it, the existence of which has been hitherto unrecognised, is destroyed. In the absence of this factor from a diet in which the nitrogen is entirely supplied by the egg-white and is complete in all other respects, young rats develop a characteristic disease, associated with dermatitis and nervous symptoms.

(2) When fresh crude egg-white is dried some toxic product is formed which is responsible for the development of the symptoms when rats are fed on a diet containing dried egg-white as a sole source of protein.

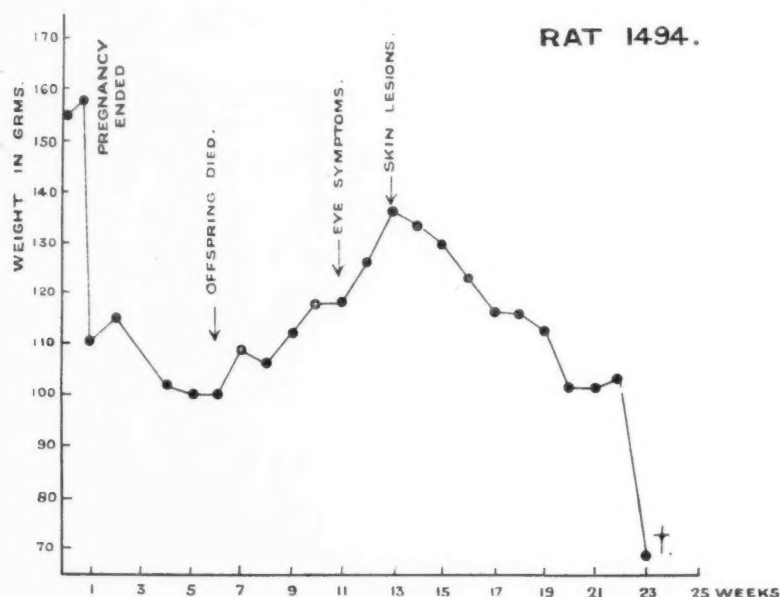
Since egg-white is the only crude protein mixture which is yet known to be susceptible to this deterioration of its nutritive properties on drying, it

appeared to be of importance to determine whether it was possible to produce the 'pink disease' syndrome in young rats by a diet which did not contain dried egg-white.

In the case of the deficiency diseases, beriberi and scurvy, it has long been known that a deficiency of the appropriate vitamin in the diet of the pregnant or lactating female results in the appearance of the deficiency disease in the suckling young, while the mother remains in apparently normal health. Thus Andrews<sup>1</sup> found that the milk of mothers who had infants suffering from beriberi produced that disease in puppies when given to them as their sole source of food, while Ingier<sup>7</sup> produced very severe scurvy in the foetal and newborn guinea-pig by feeding the mothers on a diet lacking in vitamin C. An experiment was therefore undertaken to determine the effects of placing pregnant rats on a diet capable of producing 'pink disease.' The following protocol gives the results of one such experiment.

Rat 1496 fed on dried egg white when ten days pregnant; delivered of four young at full time. The young rats began to show loss of hair when from 18 to 22 days old and died with nervous symptoms in from 28 to 35 days. Histological examination showed the characteristic

CHART II.



changes in the skin, cord and peripheral nerves. Under optimal conditions young rats cannot be weaned before the 25th day, while if deficient in vigour they usually continue to suckle for a longer period. In the present experiment the young were not observed to take any of the food themselves but were seen to suckle their mother until just before death.

There is thus evidence to show that rat's milk may give rise to 'pink disease' when the mothers are fed on dried egg-white.

Other experiments have been undertaken to determine the effects of placing female rats on the dried egg-white diet just prior to impregnation. In these experiments a normal pregnancy results, but the young are either born dead

or only survive their birth four or five days. Histological examination of these infant rats has shown cellular infiltration in the spinal cord. These experiments suggest that the 'pink disease' syndrome in the rat is a true deficiency disease analogous to beriberi or scurvy.

#### 'PINK DISEASE' SYNDROME IN ADULT RATS.

The mothers of certain of the litters which had received the diet of egg-white have continued on this régime after the death of their offspring.

Rat 1481, adult female, died after 12 weeks on the diet, having decreased from 130 gm. to 98 gm. in weight. There was loss of the long hairs on the abdomen and flanks, but no nervous symptoms. Histologically the only lesion was early round-celled infiltration of the spinal cord.

Rat 1496, adult female, after 20 weeks on the diet, had blepharitis of the right eye but no other skin symptoms and no nervous symptoms.

Rat 1494, adult female, after 13 weeks, showed loss of hair and dermatitis on the lower jaws and front of neck together with bald patches on the back. There were no nervous symptoms. The skin lesions gradually improved but the general condition became worse and after twenty-three weeks on the diet the animal died (Chart II).

Adult rats are therefore far more resistant than young rats to the effects of the dried white of egg diet, but do nevertheless develop lesions if the diet is persisted in.

#### EXPERIMENTS ON THE INFECTIVITY OF 'PINK DISEASE' IN THE RAT.

In order to exclude the possibility that 'pink disease' in the rat is due to an infection with some bacterial or ultra-microscopic organism cultures were made from the heart-blood and spleen of affected rats in broth and serum broth. The cultures were invariably sterile. Attempts to transmit the disease to normally fed rats by intraperitoneal injections of blood or emulsions of spinal cord were negative, as were the results of intra-cerebral inoculations with blood or emulsions of cord. Normally fed rats placed in the same cages as those suffering from 'pink disease' were not infected and remained in perfect health.

There is thus no experimental evidence that 'pink disease' in the rat is an infectious condition.

#### PINK DISEASE IN CHILDREN.

A brief résumé of the clinical and pathological findings in Swift's disease will now be given in order that they may be compared with those described in 'pink disease' in the rat.

*Clinical Symptoms.* The disease occurs in infants and young children aged from 4 months to 3½ years, but most commonly between 9 months and 2 years. The majority of the children are breast fed, though others may be on a mixed diet. Other members of the family are not as a rule attacked, and there is no evidence that the disease is infectious. There is usually a history of a cold some time before the onset of the disease. The condition is generally afebrile and the majority of cases eventually recover after some months, unless carried off by an intercurrent infection, such as broncho-pneumonia. According to Warthin<sup>13</sup> certain cases have recovered by forced feeding. The symptoms may be grouped under three headings (i) nutritional, (ii) cutaneous, (iii) nervous.

(i) Anorexia is constant and extreme.

(ii) The rash appears at the same time as the other symptoms. It begins as a diffuse erythema over the trunk but more especially on the extremities; the hands, feet, cheeks, nose and forehead are all affected. The skin becomes red and swollen though there is no pitting on pressure. The redness is followed by a fine desquamation especially on the palms of the hands and soles of the feet. The extremities appear extremely irritable, the child continually scratching and tearing at them, while if the face irritates he rubs it into the pillow in a burrowing manner, so that the tip of the nose becomes bright red. Ulceration of the tongue or buccal mucosa is common, but rarely extensive. The hair usually falls out in patches or is pulled out by the child, leaving large bald areas. In rare cases the nails become loose or drop off.

(iii) Although there is no evidence that the mentality of the child becomes affected he is extremely miserable and irritable: insomnia is a constant symptom. The movements are slow and there is great hypotonia of the muscles. This is shown by the lower jaw hanging down so that the mouth is open, an appearance aptly described as that of 'a young gosling.' There is no actual motor paralysis but sensation over the extremities appears to be diminished. The reflexes are either diminished or absent. According to Paterson and Greenfield<sup>9</sup> the attitude in bed is most characteristic. The child who from the first seems to show dislike of the light, keeps the face turned to the pillow. The body is in a crouching attitude, the back being curved and the knees drawn up. If the child should sit up in bed he keeps up continual movements with the upper extremities and upper part of the body. A curious mouse-like odour has been noted in most cases. There is a constant leucocytosis of from 15,000 to 40,000.

*Pathological Changes.* Comparatively few post-mortem examinations have been made but the most important findings are atrophy of the lymphoid tissues and changes in the skin, nervous system and muscles. Warthin<sup>13</sup> states that in the thymus and spleen there is a reduction of the lymphoid tissue, while the Peyer's patches and solitary glands of the intestine also exhibit a decrease in lymphocytes. Broncho-pneumonia is usually the actual cause of death.

The same observer found in the skin a reticulo-endothelial proliferation about some of the small nerve trunks, the sweat glands and hair follicles. The epidermis was hyperplastic with definite hyperkeratosis. The papillæ were enlarged and lengthened, and the capillaries of the papillæ dilated, the endothelium being swollen. The peri-vascular reticulo-endothelium was hypertrophied. Butler<sup>3</sup> found hyperkeratosis but no parakeratosis or acanthosis. The cells of the granular layer exhibited ballooning. In the corium there was considerable oedema and a lymphocytic infiltration.

Byfield<sup>4</sup> found that in the spinal cord an occasional nerve cell in the anterior horn had undergone degeneration. Some oedema was present in the sensory roots and in the myelin sheath of the sciatic nerve.

Warthin found that the main changes in the nervous system consisted of congestion and oedema of the meninges of the brain and cord, with proliferation of the reticulo-endothelial cells. Paterson and Greenfield described very definite lesions both in the central and peripheral nervous systems. In the peripheral nerves there was a considerable myelin destruction in some fibres of the peripheral nerves, increasing in degree and extent on passing to the peripheral parts of the nerves. In the central nervous system there was diffuse increase of small cells in the grey matter especially in the lumbo-sacral enlargement of the cord. The nerve roots also showed some cellular increase, but very little meningeal or perivascular exudate was found. In one case there were grave changes of the motor nerve cells of the ventral horns, particularly in those supplying the distal portions of the limbs. These changes consisted in moderate perinuclear chromatolysis with eccentricity of the nucleus, and the presence of large vacuoles in the cytoplasm of the cells. In the muscles there was considerable atrophy of the fibres, an excess of sarcolemma nuclei and an increase in the cellular content of the connective tissue septa.

By kind permission of Dr. Donald Paterson under whose care at the Hospital for Sick Children, Great Ormond Street, the child was, the courtesy of the Medical Superintendent of the North-Western Fever Hospital, where she died following an attack of measles, and the kindness of Dr. J. G. Greenfield who performed the autopsy and thereafter placed the pathological material at our disposal, we are able to refer to the pathological findings in a recent fatal case of Swift's disease.

The child, a girl, aged 1 year 7 months at the time of death, had been seen five months previously at Great Ormond Street by Dr. Paterson, who diagnosed her condition as a typical mild case of Swift's disease. There had been no definite nervous symptoms, the main complaints being those of restlessness and loss of appetite. The hands and feet were at that time the pink colour characteristic of the condition, but the general state of the child was not bad enough for institutional treatment. Five months later she developed measles and was admitted to the North Western Fever Hospital, where she died in April, 1928, of broncho-pneumonia.

At the autopsy extensive broncho-pneumonia was present in both lungs and in addition, both lungs contained minute caseous tubercles, grouped mainly around the hilus. The peribronchial lymph glands were infiltrated with tubercles, which showed early caseation on microscopic section. The heart was healthy except for two small nodules of atheroma at the base of the aorta. The liver showed early cloudy swelling. The kidneys were very congested, and microscopically the Malpighian bodies were enlarged. The tongue had a normal appearance macroscopically, but microscopically there was a slight excess of fibrous tissue throughout, with wasting of the muscle. The epithelium however was intact. The thyroid had the normal infantile appearance.

The brain and spinal cord were removed and fixed in formol saline. Portions of the gastrocnemius and triceps muscles and of the ulnar, radial, sciatic, phrenic and vagus nerves, the cervical sympathetic ganglia and the abdominal sympathetic chain were taken for section. The following staining methods were employed. Toluidin blue for Nissl granules in the brain and spinal cord, hæmatoxylin with van Gieson's counterstain, Marchi-Busch, Weigert-Pal, Bielschowsky and the Victoria blue method for neuroglia.

Above the level of the medulla, the brain appeared quite normal. In the medulla, there was a slight diffuse infiltration with small round cells, extending throughout the white and grey matter. These small cells somewhat resembled small neuroglial cells, but the neuroglia stain did not show any increase in the number of neuroglial fibres. In the spinal cord, the same infiltration was noted. It was most extensive in the grey matter of the cord and extended

along the posterior roots for some distance. The anterior roots were unaffected. The infiltration was more severe in some regions of the cord than in others. It was greatest in the eighth cervical, first and second dorsal segments and in the lumbo-sacral region. The mid-dorsal region was practically unaffected.

By the toluidin blue method the anterior horn cells appeared to be healthy for the most part. In the eighth cervical segment, the postero-lateral group of cells were seen to be rather pale. One or two of the cells in this group had eccentric nuclei and in one cell early vacuolation was seen. In the lumbo-sacral region some of the cells in the anterior horn were rounded and stained more faintly than normal, but their nuclei were central, so that the cellular change was a very early one.

Marchi and Bielschowsky preparations of the spinal cord were negative. No changes could be found in the cauda equina.

In the peripheral nerves, at first sight it seemed as though there were some demyelination of the median nerve and one of the branches of the sciatic, but both these nerves normally contain a large number of non-myelinated, sensory fibres and on comparing the median nerve with that of a normal child, no difference could be noted. All other nerves appeared well myelinated by the Weigert-Pal method.

There was no evidence of myelin degeneration by the Marchi method in any of the peripheral nerves except in one branch of the sciatic, where there was some swelling and globulation of a few nerve fibres, with some slight patchy blackening. It was difficult to be certain that this was true degeneration and not an artifact. The nerves in the muscles appeared well myelinated.

The muscles were small in bulk, but the individual fibres were not unduly wasted. They were a little smaller than normal, but had preserved their polygonal shape. There was no increase of connective tissue or fat, and the sarcolemmal nuclei were not increased in number.

The cervical sympathetic and abdominal sympathetic ganglia showed few deviations from the normal. A few cells appeared distorted in shape and had eccentric nuclei, but the majority appeared healthy. Some of the capsule cells had proliferated, but whether this was pathological is open to question. There was no cellular infiltration in the ganglia and no increase in interstitial tissue. The carotid ganglion was normal.

The slight changes in the nervous system in this case are not surprising when it is remembered that the case was clinically a mild type of the disease. The outstanding lesion, the small celled infiltration of the spinal cord corresponds exactly in extent, though in a lesser degree, with that described by Greenfield and Paterson in their three cases. This case would seem to suggest that the primary lesion is in the spinal cord and that the changes in the peripheral nervous system are secondary.

#### THE PREVENTION AND CURE OF 'PINK DISEASE' IN THE RAT.

Boas in a survey of some of the commoner food stuffs capable of preventing 'pink disease' in the rat found that raw potatoes, yeast but not marmite, raw white of egg and egg yolk were all capable of preventing the onset of the condition. These results have been confirmed. Cow's milk, however, is not very potent. Experiments which will be published elsewhere indicate that a daily ration of more than 5 c.cm. of summer milk is necessary to cure 'pink disease' in the rat. By far the most rapid cure is obtained by adding raw liver to the diet.

#### DISCUSSION.

The experiments here brought forward fully confirm the findings of Boas that when dried egg-white is fed to young rats as the sole source of protein there results a syndrome characterised by nervous and cutaneous symptoms.

The fact that the same disease may be produced by feeding the mothers on dried egg-white as the sole source of protein suggests that in the drying process some essential dietetic factor is destroyed in the egg-white, rather than that a toxic substance is formed. If the existence of a hitherto unknown dietetic factor is postulated, there is a close analogy with the known occurrence of the deficiency diseases, beriberi and scurvy in infants fed at the breast.

Investigation of the pathological changes occurring in young rats fed on dried egg-white shows that very characteristic changes occur in the central nervous system. These pathological changes still further emphasize the similarities of the condition in the rat to Swift's disease in man. These similarities may be thus briefly summarised:—

- (i). Both diseases occur in young animals. Swift's disease has never been recorded in adults, while in the adult rat it is only after from three to five months that cutaneous lesions can be produced.
- (ii). The diseases may occur on a diet of mother's milk or a ration containing ample supplies of the known vitamins.
- (iii). The clinical symptoms of both diseases are nutritional, nervous and cutaneous.
- (iv). In rats there is a characteristic 'kangaroo' position, in children a knee-elbow position.
- (v). In rats and children there is a curious mousy odour.
- (vi). Death is often due to an intercurrent broncho-pneumonia.
- (vii). There is no evidence that the diseases are due to an infection with bacteria or ultramicroscopic viruses.
- (viii). The pathological changes in the skin and nervous system are similar.

Although the possible formation of a toxic substance during the drying of egg-white cannot be excluded the experimental evidence here brought forward strongly suggests that for the normal nutrition of both young and adult rats a factor is required in addition to the known vitamins. If Swift's disease in man is identical with this new syndrome in the rat then this new factor must also play a part in human nutrition.

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# STUDIES OF PNEUMONIA IN CHILDHOOD.

## I. STATISTICAL ANALYSIS OF PNEUMONIA AND BRONCHITIS.

BY

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*Introduction.*—In a series of papers the subject of pneumonia in childhood will be presented mainly from the standpoint of morbid anatomy and histology, but with reference also to its clinical aspects. Bacteriology will not be dealt with.

In the first place, it will be an advantage to obtain a general view of the subject by means of a statistical analysis of a large series of cases, and the present paper will be devoted to this purpose. The subsequent papers will deal with the so-called lobar type of pneumonia; broncho-pneumonia; bronchiectasis; and empyema. In these studies large thin sections of the entire lung have been used, and illustrations of these will be shown. These large sections give not only an extensive view in one plane of the morbid anatomy, but also permit an accurate microscopic study of the pathological processes over a wide extent of lung.

## STATISTICAL ANALYSIS OF PNEUMONIA AND BRONCHITIS.

This analysis includes two distinct series of statistics, 648 cases of pneumonia and 244 autopsies in the same disease. The age period in both was from birth to twelve years.

The 648 cases in the clinical series were admitted to one ward of the Edinburgh Children's Hospital between January, 1921, and October, 1928, a period of almost eight years. Because of the close connection between bronchitis and pneumonia in the early years of childhood, we have placed alongside this series all cases of bronchitis admitted during the same period. A third group, bronchiectasis, includes cases where as the sequel of pneumonia or severe bronchitis there was serious and lasting damage to the bronchial walls, with bronchial dilatation in most cases and with marked fibroid change in the lung in a smaller number.

All these cases have been under one medical charge, (C. McN.). In order to secure full co-operation and exchange of views between clinician and pathologist, we have studied many of them together both in the ward and in the post-mortem room. Moreover, for the purpose of this survey, all the records have been read together by two of us, and the diagnosis and other points carefully reviewed. This revision has resulted in not a few changes;

in some instances the original diagnosis of the type of pneumonia has been modified, and doubtful cases have been excluded from the group. By this selection of a large number of cases from a single medical charge, by co-operation, and by a thorough revision of all the records, we have tried to secure uniform and consistent standards and as much accuracy as possible.

The 244 autopsies have been made and recorded throughout by one of us (A. R. M.). They include 83 examinations from the above series of 648 cases of pneumonia, and 161 examinations in cases from other wards in the hospital. The total (244) represents all cases of pneumonia examined post mortem during a period from 1st July, 1922, to 31st October, 1928.

*Main Groups in Clinical Series.*—The totals of cases and deaths in the clinical groups are shown in Table I.

TABLE I.  
MAIN GROUPS IN CLINICAL SERIES.

Disease.	Cases.	Deaths.	Death-rate.
Bronchitis .. .. .	231	6	2.5%
Pneumonia (all types and including empyema) ..	648	163	25.0%
Bronchiectasis .. .. .	33	0	0%
Totals ..	912	169	18.5%

This aggregate of 912 excludes all other respiratory diseases, *e.g.*, asthma and asthmatic bronchitis, pulmonary tuberculosis, tuberculous and rheumatic pleurisy. These figures for bronchitis and pneumonia are compared with those for all other diseases treated in the ward during the same period in Table II.

TABLE II.  
PRESENT SERIES COMPARED WITH TOTAL ADMISSIONS.

Disease.	Cases.	Deaths.	Death-rate.
Bronchitis, pneumonia, bronchiectasis .. ..	912	169	18.5%
All other cases .. .. .	1,964	380	19.5%
Totals ..	2,876	549	19%

Thus the bronchitis, pneumonia, bronchiectasis group formed 31.5 per cent. of all cases admitted. The death-rate in the same combined group was slightly lower than in the group of all other cases; while if the pneumonia group be taken alone, its death-rate was somewhat higher than in the 'all other' group.

Twenty years ago Dunlop<sup>1</sup>, in the same hospital and ward, collected and analysed 500 cases of pneumonia exclusive of empyema; the total admissions

during the same period were 3,300. A comparison with Dunlop's figures can be made by subtracting the cases of empyema from the pneumonia cases in our series (Table III).

TABLE III.  
PRESENT SERIES COMPARED WITH SERIES RECORDED IN 1908.

	PNEUMONIA.			Total Admissions.	Total Deaths.
	Cases.	Deaths.	Death-rate.		
Dunlop (1908) ..	500	104	21%	3,300	?
Present Series ..	559	127	22.5%	2,876	549

This shows that in the present series the incidence and death-rate of pneumonia were slightly higher than in a similar Edinburgh series collected some twenty years ago.

#### TYPES OF PNEUMONIA.

The types of pneumonia have been studied in two series of cases: a clinical series and a post-mortem series.

##### *Types of Pneumonia: Clinical Series.*

Table IV shows the division of the inclusive pneumonia group into its different sub-groups, giving for each the total cases and the numbers of deaths.

TABLE IV.  
CLASSIFICATION: INCLUSIVE PNEUMONIA GROUP (CLINICAL SERIES).

Type.	Cases.	Deaths.	Death-rate.
Alveolar (Lobar or Croupous) Pneumonia .. ..	386	26	7%
Broncho-pneumonia .. .. .	144	78	54%
Empyema .. .. .	89	36	40.5%
Miscellaneous Group .. .. .	21	21	100%
Acute Pleurisy .. .. .	8	2	25%
Totals ..	648	163	25%

Table IV is important and requires some explanation and discussion, especially of the clinical and pathological criteria which determined the classification. The death-rates refer to all ages between birth and twelve years and, while they are of some interest, their importance when studied in smaller age periods is much greater.

The term 'alveolar pneumonia' will be used throughout this and succeeding papers instead of 'lobar or croupous pneumonia.' The reasons for this will be given later.

The outstanding feature of the above table is the large preponderance of cases of alveolar (lobar) pneumonia over those of broncho-pneumonia. This is contrary to the majority of collected statistics of pneumonia in children. Crozer Griffith<sup>2</sup>, in a recent paper, has compared a number of statistical analyses on this point and some of these may be quoted. For example, in Dunlop's series of 265 cases of pneumonia under 2 years of age, the ratio between alveolar (lobar) and broncho-pneumonia was 1 to 5; in a similar series by Holt (322 cases) the ratio was 1 to 3. The comparable ratio in the present series (256) is 1.3 to 1. This discrepancy in results from different observers may depend partly upon climatic conditions or the type of case admitted to certain hospitals, but it is probable that a more important factor is a difference in the standards of differential diagnosis between these two types of pneumonia. It is therefore necessary to explain the standards that have been employed in the present analysis.

*Differentiation of Alveolar (lobar) and Broncho-pneumonia.* The separation of these two types of pneumonia is determined by pathological and clinical data. No bacteriological test is available. The differentiation can be made with certainty only at autopsy: during life it is more difficult and uncertain. Standard text books (*e.g.*, Holt, Thomson) give tables of symptoms and signs by which these two types may be distinguished in life. These criteria are sufficient in many cases, but in a considerable number they fail, and may even mislead, for the reason that the description of lobar pneumonia is based on the adult type, whereas the morbid anatomy of this type of pneumonia in the child often does not conform to that in the adult. In the latter, consolidation usually involves the whole of one lobe, but in children, and especially in young children, it often occupies only a small portion of a lobe. The word 'lobar' is therefore unsuited to many cases of this type in children. The pathological process, however, corresponds in its essential characters to the lobar pneumonia of the adult. The inflammation occurs in the alveoli, producing complete consolidation of a definite area; there is very little involvement of the interstitial tissue; bronchitis, if present, is no more than a trivial and superficial catarrh. We suggest that 'alveolar pneumonia' is a term which accurately describes this type of pneumonia, and that in children it is preferable to the term 'lobar' because in them the inflammation is not necessarily lobar in extent. In broncho-pneumonia, the changes are of an entirely different character. Severe bronchitis is an essential feature, with inflammatory infiltration of the bronchial wall and interstitial framework of the lung; the consolidation occurs in patches, following the distribution of the bronchial tree, with or without confluence over areas of considerable size. The word broncho-pneumonia is thus a correct description of the pathological changes in this type of pneumonia.

Does this real difference of pathological process in these two types of pneumonia manifest itself in different clinical features? The physical signs of auscultation and percussion are essential in the discovery of consolidation, and without evidence of consolidation a diagnosis of pneumonia cannot be made. A 'dry' consolidation localized in one lobe gives physical signs

characteristic of alveolar pneumonia; scattered patches of consolidation over both lower lobes, accompanied by many moist sounds, are diagnostic of broncho-pneumonia. But in two kinds of case the physical signs may be misleading. First, cases of alveolar pneumonia are met with, in which the area of consolidation is small and there are accompaniments around the pneumonic patch, and occasionally also over both roots and bases, indicating a slight catarrhal process; in such cases the physical signs closely resemble those of broncho-pneumonia. Secondly, in rapidly confluent and massive broncho-pneumonia the physical signs are very similar to those of an extensive alveolar (lobar) pneumonia. It would therefore be true to state that in the differentiation of the type of pneumonia physical signs in many cases may be of little service and may, indeed, lead to error. The manner of onset in both types may be sudden and immediately grave. It is nearly always so in alveolar pneumonia, while in broncho-pneumonia it is more often progressive; but this difference is not constant or striking. So also for the type of dyspnoea and the presence of cyanosis; they may be helpful and corroborative, but they are too inconstant to have a decisive value.

There remain, however, three things, the character of the cough, the duration of high fever and especially the type of decline of fever. These are the most important clinical features by which the two types may be distinguished. In *alveolar pneumonia*, the cough may be absent; it is, however, generally present, but it is seldom conspicuous; it is a short single cough, which may be suppressed and painful if pleurisy is present. The duration of the fever does not exceed two weeks in the great majority of cases; its level is high but not always sustained. The decline of fever is by crisis or occasionally by lysis, and is followed in most cases by equally dramatic improvement in the general condition and by rapid resolution of the exudate. In *broncho-pneumonia*, the cough is generally prominent, occurs in bouts and paroxysms, and is harsh and loud. The fever in all severe cases extends over several, and perhaps many, weeks; throughout, the temperature is apt to be irregularly remittent, although in the early stages of rapidly confluent pneumonia it may be high and sustained; in the later stages of severe cases it drops gradually and irregularly to the normal level, about which it may fluctuate for some time. We believe that in this type of pneumonia the fever almost never terminates by crisis, and only rarely by regular lysis.

These three features, the type of decline of fever, the character of the cough, and the duration of the fever, in this order of importance, have been the principal criteria by which, in doubtful cases, we have determined the type of pneumonia. Other signs and symptoms have also been of service, especially the physical signs of auscultation and percussion. The latter are, of course, necessary for the diagnosis of pneumonia, but we wish to repeat that in the differentiation of the type of pneumonia, particularly in children under two years of age, they are not seldom indecisive and misleading. And it is in these first two years, when about half of the cases of alveolar and nearly all the cases of broncho-pneumonia occur, that this separation of the two types has to be made. Whether our main clinical criteria are of the primary importance we

have assigned to them is a matter for discussion. They have been consistently applied to the present series of cases shown in Table IV, and it is probably due to them, and to the secondary place given to physical signs, that the high figures for alveolar pneumonia have been obtained.

One or two other points may be noted here. In Table I a large group of cases of bronchitis (231) is shown; of these, 192 were cases of acute bronchitis, the remainder being chronic bronchitis, laryngitis, and tracheitis. The acute cases were all febrile illnesses with cough and physical signs of bronchitis. The standards of diagnosis, in addition to the above, were the absence of consolidation and a short duration of fever. The presence of rapid and difficult respiration for a few days was not accepted as sufficient evidence of pneumonia. These more severe cases of bronchitis might, however, be regarded by other clinicians as cases of broncho-pneumonia, and in our revision we transferred from the broncho-pneumonia group to the bronchitis group a number of such cases. It must therefore be emphasized that the broncho-pneumonia group in our series has shed off into the alveolar pneumonia group on the one hand, and into the bronchitis group on the other, a number of cases that other observers with different standards would have retained within it.

*Cases of Slowly Resolving Pneumonia.* Included in the alveolar pneumonia group were 46 cases in which the process of resolution was slow, lasting from two months up to one year, or even longer in one or two instances. It might be argued that these, or some of them, were cases of broncho-pneumonia. They were carefully considered during our revision and have been retained meantime as a sub-group of alveolar pneumonia. In their onset and early course they were of the alveolar type, showing a definite, and sometimes massive, consolidation confined to one lobe or lung, but with little or no cough. In the later stages their course was almost afebrile with a satisfactory general condition. The death-rate was trifling, *viz.*, one case. Nevertheless, it seems likely that the interstitial framework had become the seat of a degree of chronic inflammation. They form an interesting group which deserves further study.

*Empyema Group.* It is hardly necessary to justify the inclusion of cases of empyema in the general consideration of a large series of cases of pneumonia in childhood, although in some published series this has not been done. In our survey we have taken out of the main groups of alveolar and broncho-pneumonia, and placed in the group of empyema, all cases in which pus or sero-purulent fluid, even in small amount, was found free in the pleural cavity before or after death. Only in this way can an accurate estimate of the frequency of this complication in pneumonia be obtained. Even so, the incidence of empyema will be under-stated by the omission of a few recovered cases in which, undetected, a slight purulent effusion had taken place and had been absorbed, and of a larger number of fatal cases in which no autopsy was made. The frequency of empyema in our aggregate group of pneumonias was 1 in 7 (89 to 648). The attempt was made to determine for all these cases of

empyema whether the original pneumonia had been alveolar or broncho-pneumonia. In 31 cases it was not possible to say; in the remaining 58 cases, the type was presumed to be alveolar in 45 and broncho-pneumonia in 13.

The death-rate in our cases of empyema at all ages was 40.5 per cent. This, however, is not a true estimate. The point will be discussed in a later section when the frequency and the death-rate of empyema over smaller age periods will be given, but the fallacy may be briefly alluded to now. In many cases of fatal empyema in infants the purulent effusion is only incidental, and the death of the child is really due to the predominant and severe pneumonia which accompanies it. For this reason the death-rate for empyema just given is inaccurate, and is too high.

*Pleurisy.* This was a small group where there was a fibrinous pleurisy without evidence of pneumonia. In several of these, pneumonia was suspected, but no convincing evidence was obtained either clinically or post-mortem. The smallness of the group is interesting, and shows how uncommon is the occurrence of primary pleurisy apart from associated inflammation of the lung.

*Miscellaneous Group.* All these were fatal cases and included various small sub-groups, terminal pneumonia, early fatal pneumonia, and other indefinite cases. These various sub-groups will be more suitably discussed in the section dealing with the post-mortem series.

#### *Types of Pneumonia: Post-mortem Series.*

During the period from 1st July, 1922, to 31st October, 1928, the total number of post-mortem examinations carried out in the hospital was 946. Pneumonia was present in 233 of these, and empyema without recognizable pneumonia in an additional 11 cases. The total number of cases of pneumonia and empyema was therefore 244, almost 26 per cent. of all autopsies.

An attempt has been made to classify the 233 cases of pneumonia according to type. In doing this both macroscopic and microscopic characters have been considered in a large number of the cases. In others, microscopic material not being available, it was necessary to rely upon the gross characters alone; but as few cases of doubtful type were among these and very careful records had been kept, it is perhaps legitimate to claim that even these could be classified with reasonable confidence. In a large series of cases occurring after the end of 1925, in addition to ordinary microscopic material, paraffin sections of whole lungs have been used. The result is shown in Table V.

We do not intend to discuss fully in this paper the pathological grounds on which the types have been distinguished, because that will form an important part of later communications. A brief reference has already been made to the chief pathological features of alveolar and broncho-pneumonia (p. 15).

*Broncho-pneumonia.* The immense preponderance of broncho-pneumonia over all other forms is a striking illustration of the fatal character of this type. It is not, however, to be regarded as proving that this is the commonest type of pneumonia at any age period. It must not be forgotten that the cases included in any post-mortem series are in a sense selected cases, selected, that

is to say, by the fatality of the disease. The frequency with which any type of pneumonia is seen in the post-mortem room is no measure of its actual incidence. Nevertheless this group must be regarded as the most important, because it is clear from a consideration of the figures presented in Table V, that the pressing problem of pneumonia mortality is in very large measure a problem of broncho-pneumonia.

TABLE V.  
CLASSIFICATION : ALL CASES (POST-MORTEM SERIES).

Type.	Number.
Broncho-pneumonia .. .. .	140
Alveolar (lobar) pneumonia .. .. .	23
Terminal pneumonia .. .. .	29
Miscellaneous group .. .. .	15
Chronic pneumonia .. .. .	5
Septic (pyæmic) pneumonia .. .. .	4
Unclassified .. .. .	17
Empyema without pneumonia .. .. .	11
Total ..	244

*Alveolar (lobar) pneumonia* was represented by a small group of 23 cases. This is in striking contrast to the numerical superiority of this type in our clinical series. The relatively low mortality of alveolar pneumonia in children causes it to occupy a subsidiary place in a series of post-mortem cases.

There were several cases in which appearances characteristic both of alveolar and of broncho-pneumonia were present in different parts of the lungs. These have been classed as broncho-pneumonia.

*Terminal pneumonia.* The cases classed as terminal pneumonia might be regarded as a sub-group of broncho-pneumonia, with which they had certain features in common. They were mostly cases of hypostatic pneumonia in marasmic infants or debilitated children with enteritis or other wasting diseases. In most instances clinical manifestations of pneumonia were not present; consolidation was posterior and basal in distribution, somewhat indefinite in character, and associated with marked passive congestion and oedema.

*Miscellaneous Group.* Although the great majority of the acute cases fell into one of the above groups, there were a few whose characters did not justify their inclusion under the name of either alveolar or broncho-pneumonia. These are included in Table V in a miscellaneous group which embraces cases of three different types, as follows :—

First, there was a group of four cases, all in infants under one month old, in which the microscopic changes consisted of very intense generalized congestion and rather massive consolidation in both lungs, without much inflammation of the bronchi. The appearance resembled that of the condition which Gaskell<sup>3</sup> has called 'miliary pneumonia' and ascribes to an infection reaching the lungs *via* the blood stream. Microscopically, the presence of a copious exudate of polymorphonuclear leucocytes was somewhat at variance with Gaskell's description. Whether or not these cases may be regarded as examples of this blood-spread type of pneumonia, they were certainly not ordinary broncho-pneumonia; nor could they be legitimately classed as alveolar pneumonia.

Secondly, there were five cases which resembled those described by M'Gowan and McNeil<sup>4</sup> in 1913. In all of these the illness lasted less than twenty-four hours; the symptoms were those of an acute respiratory infection; the lungs showed quite an extraordinary degree of active hyperæmia, some œdema, but no consolidation; and in four of the five cases there was general hyperplasia of lymphoid tissue throughout the body, with or without enlargement of the thymus gland.

Thirdly, six cases showed widespread patches of consolidation in both lungs, not obviously related to the distribution of bronchi, and an absence of generalized bronchitis and of interstitial inflammation of the bronchial walls and pulmonary stroma. The appearance was that of the so-called 'lobular' or 'primary disseminated pneumonia.' Holt<sup>5</sup>, who describes this type fully, states that it is the commonest form of pneumonia in infancy and is attended by a mortality of about sixty per cent. in the first two years of life. In view of this, we have been surprised to find in our series so few cases corresponding to his description. It would seem that either the incidence or the mortality of this type must be much less in this locality than in Holt's experience.

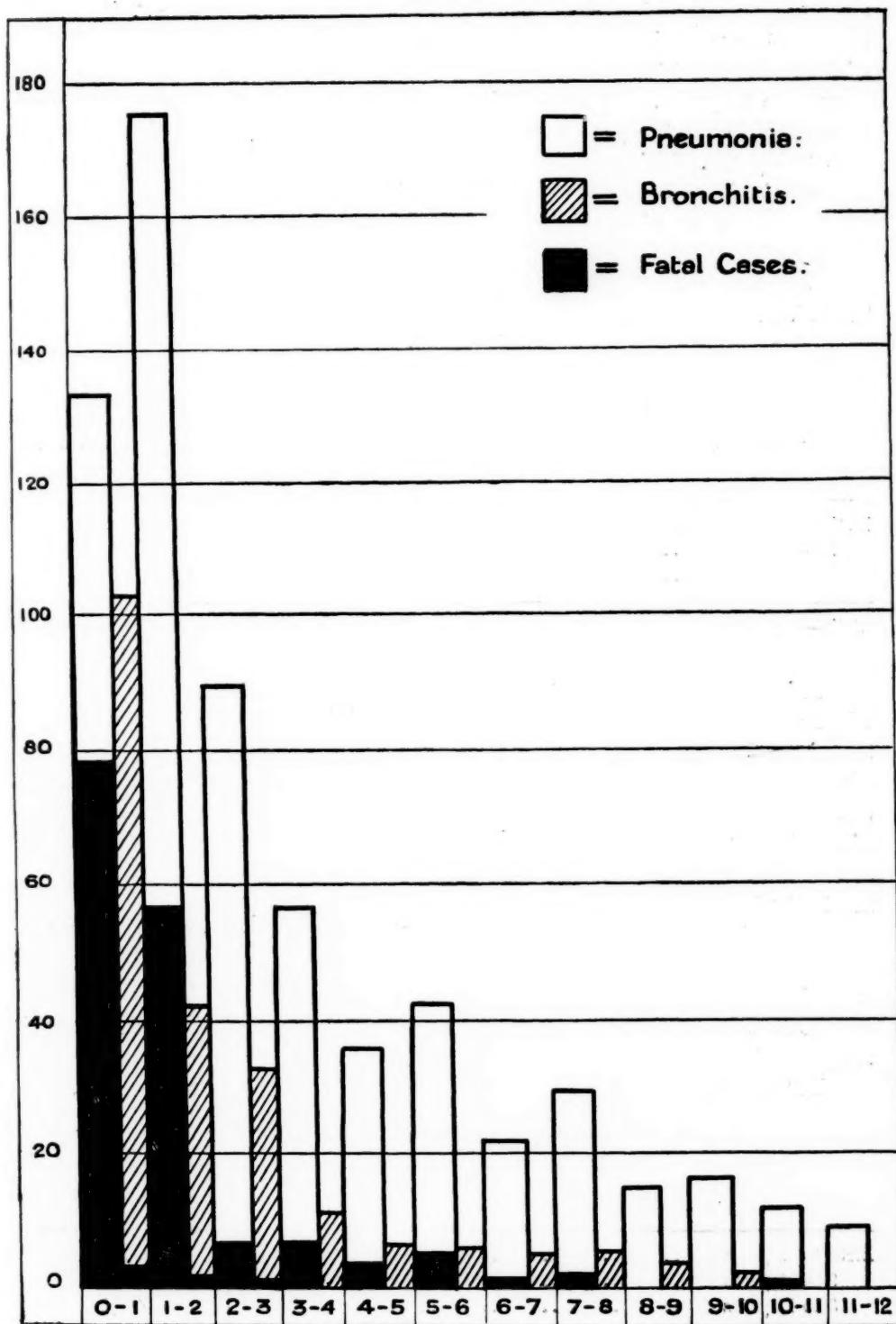
The small group called *chronic pneumonia* includes cases of organising pneumonia, pulmonary fibrosis and bronchiectasis. The *septic or pyæmic pneumonias* were cases of septicæmia and pyæmia in which pneumonia occurred as a secondary manifestation of a general pyogenic infection.

The seventeen *unclassified* cases showed remnants of pneumonia post mortem, but it was impossible to determine with reasonable accuracy of what type the pneumonia had been. Most of them were cases of empyema, or of death from other complications or sequelæ, such as pericarditis, in which the original pneumonia had all but completely resolved.

#### THE INFLUENCE OF AGE ON THE INCIDENCE AND DEATH-RATE OF PNEUMONIA AND BRONCHITIS.

The factor of age is of great importance and interest. As regards the *clinical series*, its influence is shown graphically in Chart I. In it the numbers of cases of pneumonia and of bronchitis, and also the deaths, are represented for one-yearly periods throughout childhood. All types of pneumonia and empyema, as set out in Table IV, are merged into one inclusive group.

CHART I.



AGE INCIDENCE: ALL CASES (CLINICAL SERIES).

Taking pneumonia, it will be seen that the totals reach their highest peaks in the first two years; they then fall rapidly until the fifth year and more slowly in subsequent years. The deaths from pneumonia are concentrated in the first two years in a remarkable way; indeed, in the first year the number of deaths is almost three times, and in the second year it is quite twice, the total from 2 to 12 years. The cases of bronchitis, numbering 231, show a similar distribution over the yearly age periods, the great mass being found in the first two years. This parallel behaviour of the two diseases, bronchitis and pneumonia, is most significant and interesting.

The influence of age in pneumonia and bronchitis can be emphasized by grouping the twelve one-yearly periods into three larger ones, birth to 2 years, 2 to 5 years, and 5 to 12 years. When this is done, the figures shown in Table VI are obtained.

TABLE VI.  
AGE-GROUPS IN CLINICAL SERIES.

Age Group.	PNEUMONIA.			BRONCHITIS.		
	Cases.	Deaths.	Death-rate.	Cases.	Deaths.	Death-rate.
Birth— 2 years ..	310	136	44%	155	5	3%
2— 5 years ..	184	18	10%	55	1	2%
5—12 years ..	154	9	6%	21	0	0%
Birth—12 years ..	648	163	25%	231	6	2.5%

This grouping brings into prominence the period of the first two years, when the remarkable concentration of cases of pneumonia and of deaths therefrom is apparent. One half of all cases of pneumonia and five-sixths of the deaths occur at this time. It is again worth noting that in this grouping the behaviour of bronchitis is closely parallel, two-thirds of the cases and five of the six deaths falling within the first two years. This period therefore stands out as one of special susceptibility to bronchitis and pneumonia, and of high mortality from the latter.

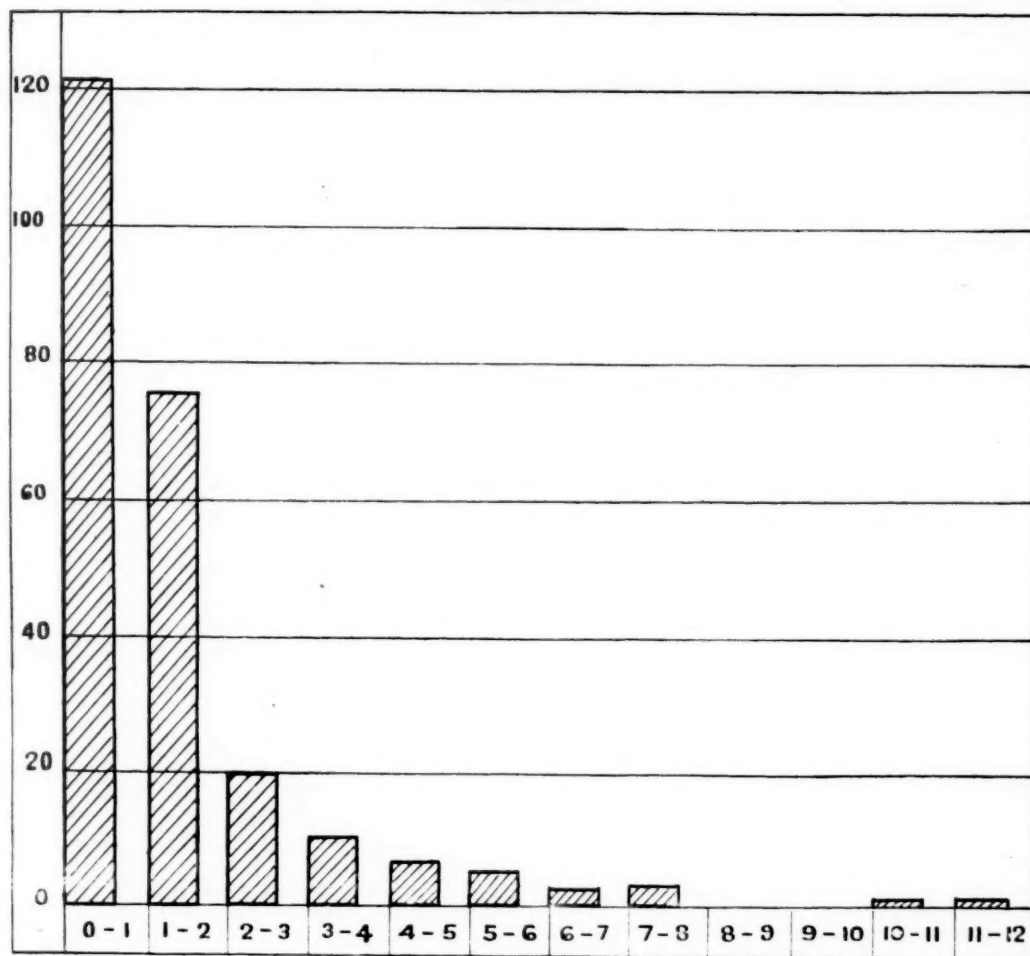
These facts regarding the influence of age on mortality receive striking confirmation from a study of the age incidence in the *post-mortem series*, which comprises a larger number of fatal cases than the clinical series. Chart II represents the number of deaths in the combined group of pneumonia and empyema in one-yearly periods.

In Table VII, the deaths are grouped in the three larger age-periods.

TABLE VII.  
AGE-GROUPS: POST-MORTEM SERIES.

Age Group.						Deaths.	Percentage of Total.
Birth to 2 years	..	..	..	..	..	196	80.5%
2 to 5 years	..	..	..	..	..	36	15%
5 to 12 years	..	..	..	..	..	11	4.5%
Birth to 12 years	..	..	..	..	..	243	—

CHART II.



AGE INCIDENCE: ALL CASES (POST-MORTEM SERIES).

The high mortality in the first two years and the rapid decrease in the later age periods are very clearly shown. In Chart II it may be noted that almost one half of all the deaths occurred in the first year.

It is worth while tracing in half-yearly periods the death-rates for pneumonia in the *clinical series* through this critical time of the first two years (Table VIII).

TABLE VIII.  
INCLUSIVE PNEUMONIA GROUP (CLINICAL SERIES).

Age Group.	Cases.	Deaths.	Death-rate.
Birth to 6 months .. ..	45	40	89%
6 to 12 months .. ..	89	39	45%
1 to 1½ years .. ..	91	34	37.5%
1½ to 2 years .. ..	85	23	27%
2 to 3 years .. ..	90	9	10%

The numbers of cases in each period are sufficient to allow comparison by a percentage death-rate. The rate shows a regular decline from a very high figure in the first six months. In the third year the rate has dropped to 10 per cent., which is that of the whole period 2 to 5 years.

Table IX shows the number of deaths from pneumonia and empyema in the *post-mortem series* in the first four half-yearly periods.

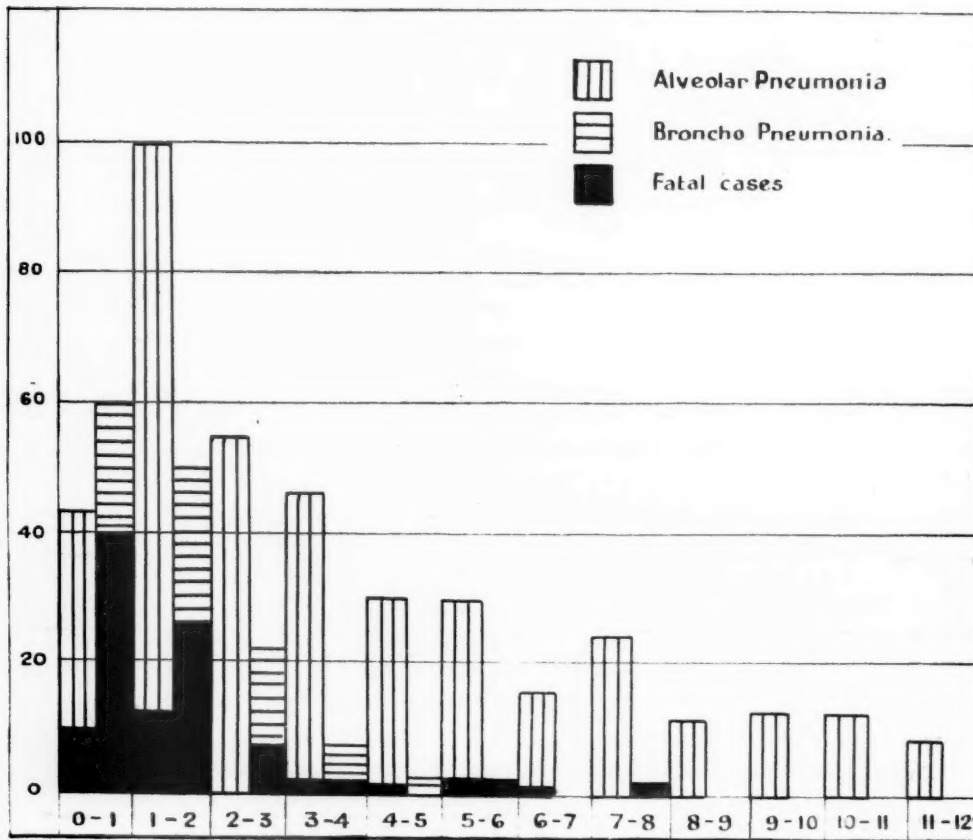
TABLE IX.  
AGE GROUPS: PNEUMONIA AND EMPYEMA (POST-MORTEM SERIES).

Age Period.	Deaths.	Percentage of Total.
Birth to 6 months .. .. .	64	26%
6 to 12 months .. .. .	57	23.5%
1 to 1½ years .. .. .	55	23%
1½ to 2 years .. .. .	20	8%

These figures are in agreement with those of the clinical series. The largest number of fatal cases was in the first half-year and a steady fall occurred thereafter. There was a remarkable decrease in numbers after the age of eighteen months.

*Alveolar and Broncho-pneumonia.* The influence of age in these separate groups in the *clinical series* is illustrated in Chart III. It should be noted that they do not contain cases of empyema or of the miscellaneous group.

CHART III.



AGE INCIDENCE: COMPARISON OF ALVEOLAR AND BRONCHO-PNEUMONIA (CLINICAL SERIES).

The broncho-pneumonia group may be taken first. Here the broad result is simple and striking: the great majority both of cases and deaths occurred in the first two years—about 80 per cent. of the cases and 84 per cent. of the deaths. There were only three cases after the fifth year, all of them fatal. Thus, in the clinical series the death-rate for this type of pneumonia was high throughout the whole period of childhood.

The results for alveolar pneumonia are different, both in case-incidence and death-rates. Considerably less than half the cases occurred in the first two years (38 per cent.). This type, indeed, was fairly common throughout childhood, although the numbers, measured in yearly periods, fell off after the fourth year. With regard to deaths, although again the great majority (about 80 per cent.) occurred in the first two years, the death-rate for this period was trifling (14.5 per cent.) as compared with that for broncho-pneumonia (61 per cent.); thereafter, it at once fell to a low level, at which it remained throughout childhood.

These broad results can be shown clearly in figures by the use of larger age periods (Table X).

TABLE X.

AGE GROUPS: CLINICAL SERIES.

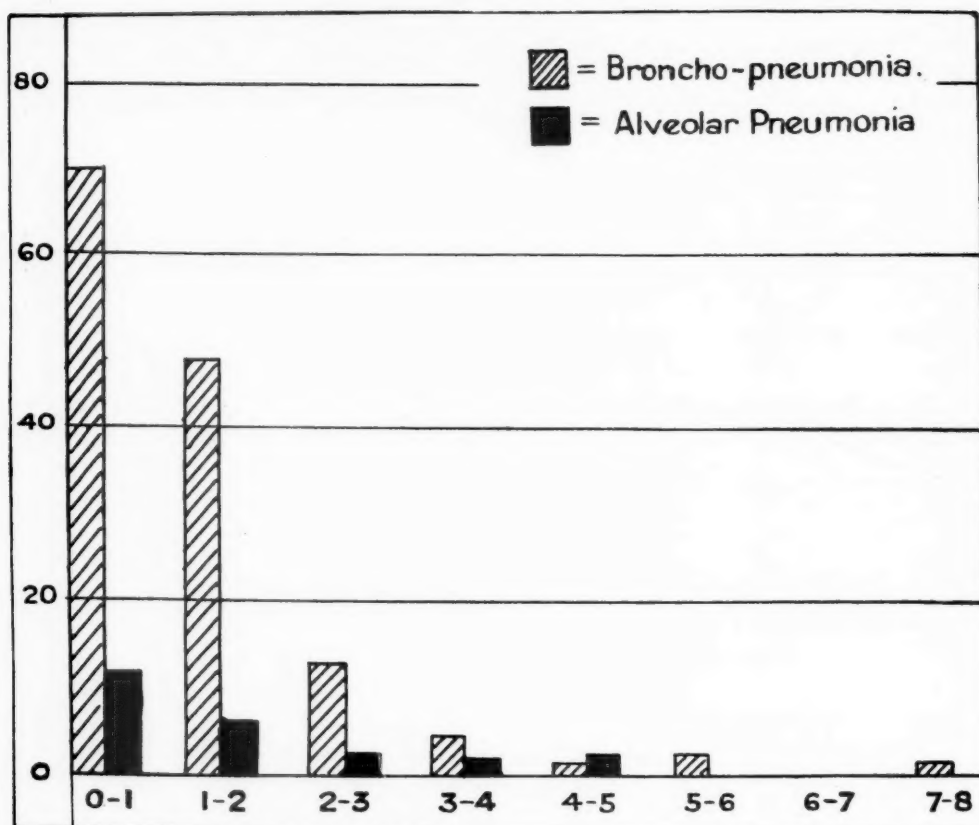
Age Group.	ALVEOLAR PNEUMONIA.			BRONCHO-PNEUMONIA.		
	Cases.	Deaths.	Death-rate.	Cases.	Deaths.	Death-rate.
Birth to 2 years ..	143	21	14.5%	110	67	61%
2 to 5 years ..	131	2	1.5%	31	8	26%
5 to 12 years ..	112	3	2.5%	3	3	100%
Birth to 12 years ..	386	26	6.5%	144	78	54%

It should be mentioned that the death-rates given above are lower than they should be, especially for broncho-pneumonia, by the omission of cases of empyema and of the miscellaneous group.

Chart IV represents the age incidence in the *post-mortem series* of alveolar and broncho-pneumonia in yearly periods.

It confirms the facts obtained from the clinical series. In the earlier age periods the fatal cases of broncho-pneumonia show a vast preponderance over those of alveolar pneumonia. Nevertheless, the two curves are not materially different in form. Further, in both types of pneumonia, the period of greatest mortality is the first year.

CHART IV.



AGE INCIDENCE: COMPARISON OF ALVEOLAR AND BRONCHO-PNEUMONIA (POST-MORTEM SERIES).

*Empyema.* The standards of selection for this group have already been explained. The aim was to include all cases in which any pus or sero-purulent fluid, discovered by needle-aspiration during life or by post-mortem examination, had been poured out into the pleural cavity. The total was 89, but as the number for annual periods were small, the influence of age will be better shown by taking the longer periods previously used (Table XI).

TABLE XI.

AGE GROUPS: EMPYEMA (CLINICAL SERIES).

Age Group.	Cases.	Deaths.	Death-rate.
Birth to 2 years .. .. .	36	27	75%
2 to 5 years .. .. .	19	6	31.5%
5 to 12 years .. .. .	34	3	8.5%
Birth to 12 years .. .. .	89	36	40.5%

The incidence of empyema would appear by Table XI to be fairly equal in the three periods. It must be remembered, however, that empyema is not an independent disease, but a complication of pneumonia. What it is really important to ascertain is the frequency of its occurrence in pneumonia; and to do this, the figures for empyema must be set alongside those for pneumonia in the same age periods. This comparison is made in Table XII.

TABLE XII.  
AGE GROUPS: (CLINICAL SERIES).

Age Group.	Pneumonia (all cases including empyema).	Empyema.	Empyema percentage.
Birth to 2 years .. .. .	310	36	11.5%
2 to 5 years .. .. .	184	19	10.5%
5 to 12 years .. .. .	154	34	22%
Birth to 12 years .. .. .	648	89	13.5%

The result brought out by these figures is definite. The complication of empyema is twice as frequent in pneumonia after five years as before that age. In the present series empyema occurred once in every five cases of pneumonia over five years of age. Some allowance must, however, be made for fatal cases of pneumonia where empyema was undetected during life and where no post-mortem examination was made; but even if this is done, the broad statement is probably true that the complication of empyema is decidedly commoner in pneumonia after five years of age than before it. Over the whole period, the frequency of empyema in pneumonia was about one in seven.

With regard to the death-rates for empyema in these age periods, it must be repeated that empyema is a complication of an acute and death-producing disease, and that in early childhood the death-rate from pneumonia alone is very high. Therefore, the figures for the first two years in Table XI do not accurately express death-rates from empyema. No doubt the occurrence of empyema is an added risk of death, but the risk from the existing pneumonia is already great. In the period 5 to 12 years, when the death-rate from pneumonia is trifling, the death-rate for empyema given above is approximately accurate.

#### SEX INCIDENCE.

The influence of sex is shown in Tables XII and XIII.

TABLE XII.  
SEX INCIDENCE: ALL CASES (CLINICAL SERIES).

Type.	Male.	Female.
Bronchitis .. .. .	126	105
Alveolar pneumonia .. .. .	230	156
Broncho-pneumonia .. .. .	79	65
Miscellaneous group .. .. .	15	6
Empyema .. .. .	53	36
Pleurisy .. .. .	6	2
Bronchiectasis .. .. .	11	22
Totals ..	520	392

TABLE XIII.

SEX INCIDENCE: ALL CASES (POST-MORTEM SERIES).

Types.	Male.	Female.
Alveolar pneumonia .. .. .	17	6
Broncho-pneumonia .. .. .	78	62
Terminal pneumonia .. .. .	21	8
Miscellaneous group .. .. .	11	4
Chronic pneumonia .. .. .	2	3
Septic (pyæmic) pneumonia .. .. .	3	1
Unclassified .. .. .	10	7
Empyema (no pneumonia) .. .. .	7	4
Totals ..	149	95

The noteworthy feature of these figures is the preponderance of males. It is remarkably consistent throughout the different groups. The total for males for both series is 669 as against 487 for females, a ratio of 1.37 to 1. The only exceptions are found in the bronchiectasis group in the clinical series, and in the chronic pneumonia group in the post-mortem series; it is interesting and perhaps significant that these two are the only chronic groups represented in the tables.

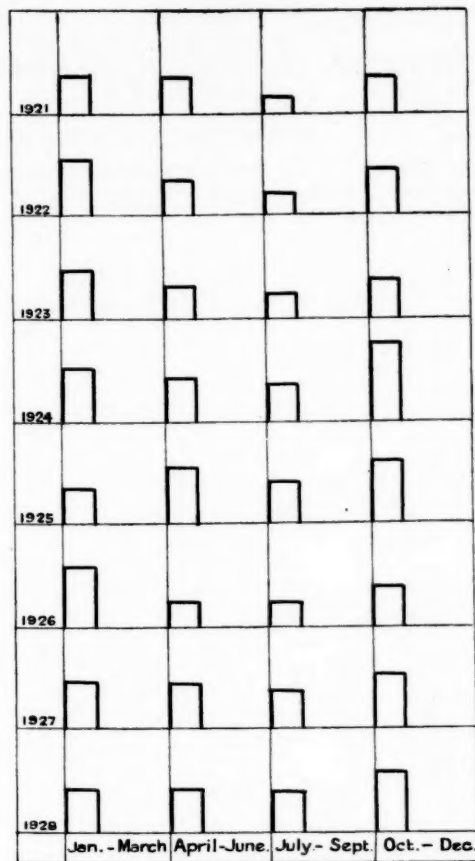
## SEASONAL INCIDENCE.

Charts V, VI and VII illustrate the influence of season. The figures in Charts V and VI include cases admitted till the end of 1928, thus bringing a period of eight complete years under review and differing slightly from the remainder of the clinical statistics which do not go beyond 31st October, 1928.

Chart V shows the quarterly incidence of pneumonia (all types and including empyema) in each of the eight years. From it the total yearly incidence can be roughly judged and it is seen that there is no very significant difference between the years, the totals ranging from a minimum of 63 in 1921 to a maximum of 105 in 1924. This chart and the succeeding one (Chart VI), which includes bronchitis in addition to pneumonia, also illustrate the relative importance of the seasons. The numbers of cases of both pneumonia and bronchitis were, of course, greater in the autumn and winter months, but it is to be noted that throughout the period of eight years the incidence of these two acute respiratory diseases never became negligible in any one month or quarter of the year.

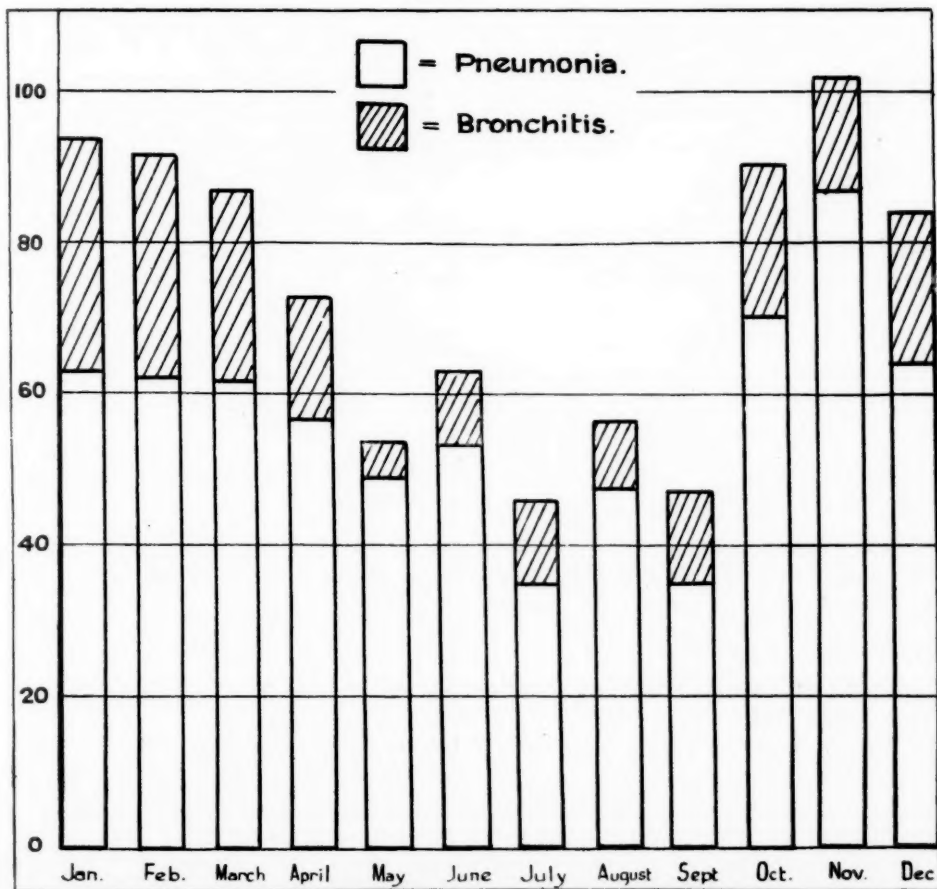
When the figures are further considered over quarterly periods, it is found that in the case of pneumonia the average is highest in the fourth (October-December) and is only slightly less in the first (January-March) quarter: it is lowest in the third (July-September) quarter. A similar variation is shown in the post-mortem series (Chart VII). It is perhaps worthy of remark that the first quarter of the year, which can be regarded as the second half of the winter, might have been expected to provide the greatest number of cases, and especially of fatal cases, of pneumonia.

CHART V.



QUARTERLY INCIDENCE: PNEUMONIA (CLINICAL SERIES).

CHART VI.



TOTAL MONTHLY INCIDENCE (CLINICAL SERIES).

Chart VI gives the total monthly incidence of pneumonia and bronchitis over the whole period of eight years. Of the individual months in this (clinical) series, November shows the highest, and July and September the lowest incidence of pneumonia. The seasonal occurrence of bronchitis is slightly different: the rate is highest in January and February, with the result that the first quarter (January—March) shows the greatest number of cases.

CHART VII.

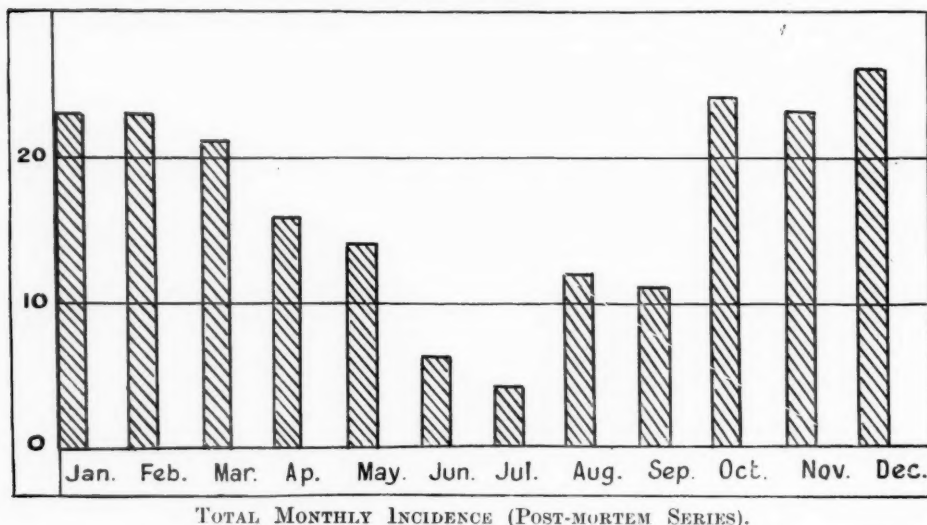


Chart VII illustrates the total monthly incidence of fatal cases in the post-mortem series. In order to enable six complete years to be reviewed, the period 1st November, 1922, to 31st October, 1928, has been taken: it differs slightly from that covered by the remainder of the post-mortem statistics (1st July, 1922 to 31st October, 1928). This Chart is more striking than the similar clinical one (Chart VI) and the contrasts are greater. The two correspond, as has already been mentioned, in that in both the fourth (October—December) quarter shows the highest figures. While, however, in the clinical series November had the highest incidence of pneumonia, December was the month in which autopsies were most numerous.

In conclusion we wish to express our thanks to our colleagues, Dr. N. S. Carmichael and Dr. L. H. F. Thatcher, for their courtesy in putting at our disposal a number of their fatal cases of pneumonia. These have been included in the post-mortem series dealt with in this paper. In subsequent papers we shall again be indebted to them for clinical records and post-mortem material in other cases that were under their care.

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## APPENDIX.

The three following Tables contain a detailed statement regarding age incidence in both the clinical and post-mortem series: and facts regarding the site of consolidation in the post-mortem series.

TABLE XIV.  
AGE INCIDENCE: ALL CASES (CLINICAL SERIES).

Type.	Age in years.	0— $\frac{1}{2}$	$\frac{1}{2}$ —1	1—1 $\frac{1}{2}$	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—9	9—10	10—11	11—12
Bronchitis ..	Total	56	47	33	19	33	13	9	6	5	5	3	2	—	—
	Deaths	3	—	1	1	1	—	—	—	—	—	—	—	—	—
Alveolar pneumonia	Total	3	40	47	53	45	46	30	30	15	24	11	12	12	8
	Deaths	1	8	6	6	—	1	1	2	1	—	—	—	—	—
Broncho-pneumonia	Total	25	35	31	19	22	7	2	2	—	1	—	—	—	—
	Deaths	22	19	18	8	7	1	—	2	—	1	—	—	—	—
Empyema ..	Total	6	9	9	12	12	4	3	10	7	5	4	5	1	2
	Deaths	6	7	6	8	1	4	1	1	—	1	—	—	1	—
Pleurisy ..	Total	—	1	—	1	—	1	1	1	—	—	1	1	1	—
	Deaths	—	1	—	1	—	—	—	—	—	—	—	—	—	—
Miscellaneous	Total	11	4	4	—	1	—	1	—	—	—	—	—	—	—
	Deaths	11	4	4	—	1	—	1	—	—	—	—	—	—	—
Bronchiectasis	Total	3	5	6	1	6	6	2	2	—	1	1	—	—	—
	Deaths	—	—	—	—	—	—	—	—	—	—	—	—	—	—

TABLE XV.  
AGE INCIDENCE: ALL CASES (POST-MORTEM SERIES).

Type.	Age in years.	0— $\frac{1}{2}$	$\frac{1}{2}$ —1	1—1 $\frac{1}{2}$	1 $\frac{1}{2}$ —2	2—3	3—4	4—5	5—6	6—7	7—8	8—9	9—10	10—11	11—12
Broncho-pneumonia		33	37	38	10	13	4	1	2	—	1	—	—	—	—
Alveolar pneumonia		3	9	4	2	2	1	2	—	—	—	—	—	—	—
Terminal pneumonia		19	3	3	2	1	—	1	—	—	—	—	—	—	—
Miscellaneous group		7	4	2	1	1	—	—	—	—	—	—	—	—	—
Chronic pneumonia		—	—	2	—	—	2	—	—	1	—	—	—	—	—
Septic (pyæmic) pneumonia ..		—	—	—	—	—	1	—	—	—	1	—	—	1	1
Unclassified .. ..		1	2	4	3	1	1	1	2	1	1	—	—	—	—
Empyema (no pneumonia) ..		1	2	2	2	2	1	1	—	—	—	—	—	—	—
Total ..		64	57	55	20	20	10	6	4	2	3	0	0	1	1

TABLE XVI.

SITE; ALL CASES (POST-MORTEM SERIES).

Type.	Right.	Left.	Both.
Broncho-pneumonia .. ..	20	8	112
Alveolar pneumonia .. ..	8	8	7
Terminal pneumonia .. ..	1	3	25
Miscellaneous group .. ..	0	0	15
Chronic pneumonia .. ..	0	1	4
Septic (pyæmic) pneumonia ..	0	1	3
Unclassified .. ..	5	8	4
Empyema (no pneumonia) .. ..	3	4	4
Total ..	37	33	174

# RACIAL VARIATION IN RELATION TO INFANT MORTALITY IN THE FOUR PRINCIPAL SCOTTISH TOWNS.

BY

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In the course of a detailed investigation of the infant mortality statistics of Aberdeen from 1856 to 1926, and of the various factors which might be considered to have a bearing on this mortality, including a comparison of the conditions of life in the four principal Scottish towns, it was discovered that the infant deaths from developmental causes formed the most important group. It is proposed first to indicate briefly the general findings of the investigation before discussing in detail the mortality in the four principal Scottish towns from the group of developmental diseases, and the effect which changes in the racial composition of the towns may have had on this mortality.

Aberdeen's relatively high infant mortality in recent years has been a puzzle in Scottish infant mortality statistics. A review of the infant mortality rates of the four principal Scottish towns from 1856 to 1926 only emphasizes the problem, for in the earlier years Aberdeen had the lowest infant mortality of the four, the 1856-60 rates being Aberdeen 126, Edinburgh 146, Dundee 169, Glasgow 175. It first lost this superiority in the 1886-95 decennium, and in 1921-25 its rate is actually the highest of the four, the figures being Edinburgh 91, Glasgow 107, Dundee 113, Aberdeen 115. The Glasgow experience in infant mortality differs from that of Aberdeen, Dundee and Edinburgh, in that the trend in Glasgow shows a much more uniform fall than is the case in the other three towns. It is noteworthy also that at a period (1886-90) when the other three towns exhibited a marked increase in infant mortality, the Glasgow rate decreased considerably; and it is interesting to find that at the period in question Glasgow was admittedly the most insanitary of the four towns. Indeed, an examination of the housing conditions throughout the period under review proves that Glasgow has had the greatest degree of overcrowding, both of site and of rooms, and Aberdeen the least. As regards domestic sanitation, Aberdeen is in the most favourable position of the four, and Dundee in the least.

Comparison of the birth rates of Aberdeen and Glasgow reveals the fact that Glasgow has had a higher birth rate than Aberdeen throughout the period under review, and the experience of these two towns does not, therefore, support the prevalent idea that a high birth rate is a factor in the production of a high infant mortality.

Analysis by age periods of the infant mortality of the four towns demonstrates that the 6-12 months age period is the only one in which there is distinct improvement in all four towns. It appears also that it is the 0-3 months mortality rate which establishes the superiority of Edinburgh and Glasgow over Aberdeen and Dundee. Finally, the fact that the Aberdeen 0-3 months mortality shows an increase of 7 per cent. as against a decrease in the other three towns, gives a clue as to which group of diseases is operating against the decrease of infant mortality in Aberdeen.

# I. INFANT MORTALITY FROM DEVELOPMENTAL DISEASES IN THE FOUR PRINCIPAL SCOTTISH TOWNS (1856 TO 1925).

This group of 'developmental diseases' includes all causes which may be stated to have a pre-natal or intra-natal origin, namely premature birth, atrophy, congenital debility, marasmus, icterus, sclerema, congenital malformations, injury at birth, and other diseases peculiar to early infancy, chiefly atelectasis and diseases of the umbilicus. It has no claim to be a homogeneous group. Injury at birth, for example, has not necessarily any causal relationship with prematurity, but it is considered that the group, as a whole, forms a better basis for comparison, and at least one source of error, due to transference of causes from one sub-group to another, is eliminated. Chalmers' illustrates the extent to which this transference appears to have occurred in Glasgow. The proportion of deaths in the first month of life ascribed to premature birth, congenital defects, and atelectasis, increased by 12 per cent. from 1903-1907 to 1908-1912, the proportion to atrophy and debility decreased by 27 per cent., whereas the two together decreased by only 1.4 per cent.

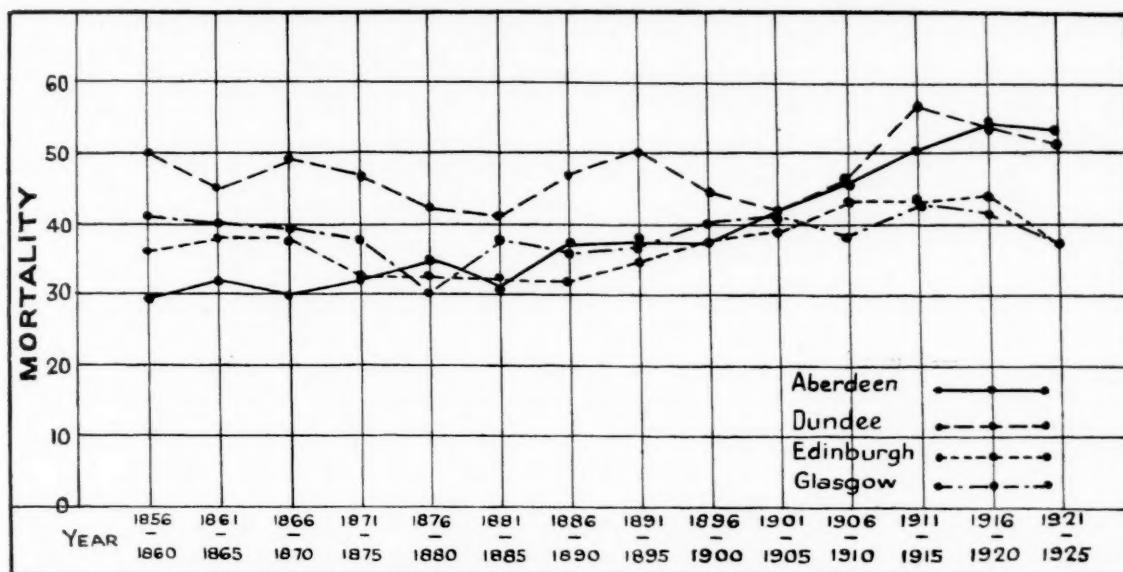
Table I and Chart I show the infant mortality from the developmental group in the four principal Scottish towns from 1856-1925, in five-yearly averages.

TABLE I.  
INFANT MORTALITY FROM GROUP OF DEVELOPMENTAL DISEASES IN THE  
FOUR PRINCIPAL SCOTTISH TOWNS, 1856-1925.

YEAR. Mean of :	ABERDEEN.			DUNDEE.			EDINBURGH.			GLASGOW.		
	No. of births.	No. of deaths.	Mortality rate.	No. of births.	No. of deaths.	Mortality rate.	No. of births.	No. of deaths.	Mortality rate.	No. of births.	No. of deaths.	Mortality rate.
1856-1860	2,397	71	29.6	3,474	174	50.0	5,337	195	36.5	15,729	649	41.2
1861-1865	2,663	86	32.3	3,923	178	45.3	6,003	229	38.1	16,878	686	40.6
1866-1870	3,010	91	30.2	4,496	221	49.3	6,566	253	38.5	18,618	744	39.9
1871-1875	3,169	103	32.5	4,907	231	47.0	6,779	226	33.3	19,875	750	37.7
1876-1880	3,480	123	35.3	5,115	217	42.4	7,337	240	32.7	20,278	715	30.5
1881-1885	3,712	116	31.3	4,980	207	41.5	7,263	235	32.3	19,834	750	37.7
1886-1890	3,827	143	37.4	4,719	223	47.2	7,417	240	32.3	19,456	707	36.3
1891-1895	4,114	155	37.7	4,797	243	50.6	7,318	255	34.8	22,326	831	37.2
1896-1900	4,636	174	37.5	4,822	221	45.0	8,010	307	38.3	24,153	983	40.6
1901-1905	4,872	205	42.1	4,618	195	42.2	7,891	308	39.0	24,626	1,012	41.0
1906-1910	4,505	207	45.9	4,557	213	46.7	7,426	324	43.6	23,568	907	38.4
*1911-1915	3,959	201	50.8	4,165	236	56.7	6,282	274	43.3	25,903	1,126	43.4
1916-1920	3,479	188	53.5	3,596	193	53.8	5,775	253	44.1	26,621	1,111	41.7
1921-1925	3,763	201	53.2	4,087	211	51.5	8,541	316	37.0	27,093	1,027	37.6

CHART I.

INFANT MORTALITY FROM GROUP OF DEVELOPMENTAL DISEASES IN THE FOUR PRINCIPAL SCOTTISH TOWNS, 1856-1925.



The first glance shows that the Aberdeen experience is different from that of the other three towns. Its rate starts well below any of the others, and climbs steadily until it attains the highest point of the four. Dundee and Edinburgh show a tendency to rise, but their increase is on a much smaller scale than that of Aberdeen. Thus Aberdeen increases from 29.6 in 1856-1860 to 53.2 in 1921-1925, an increase of 79 per cent., while Dundee increases from 50.0 to 51.5, and Edinburgh from 36.5 to 37, representing increases of 3 per cent. and 1 per cent. respectively. Glasgow is the only town which shows a decrease over the whole period, from 41.2 in 1856-1860 to 37.6 in 1921-25, a decrease of 9 per cent.

In the earlier years there is a difference of 6.9 between Aberdeen and the next lowest town, Edinburgh, their values in 1866-1870 being 30.2 and 38.5 respectively. The following quinquenniad marks the beginning of Aberdeen's upward trend, the rate in 1871-1875 reaching 32.5, which approximates the Edinburgh rate of 33.3. A further rise for Aberdeen in 1876-1880 to 35.3 takes it above both the Edinburgh and Glasgow figures, Edinburgh maintaining an almost constant level for twenty years, and Glasgow having fallen from 37.7 in 1871-1875 to 30.5 in 1876-1880. In 1886-1890 Aberdeen rises fairly sharply again to 37.4, which was Glasgow's figure in 1881-1885, and from that point the two rates run a similar course up to the end of the century. In 1901-1905 Aberdeen has reached 42.1, and Glasgow 41.0. The Edinburgh rate has been rising since 1891-1895 and in 1901-1905 it stands at 39.0. Meanwhile Dundee has maintained a fluctuating and distinctly higher rate; beginning at 50 in 1856-1860 it descends to 41.5 in 1881-1885, rises to 50.6 in 1891-1895,

and in 1901-1905 it falls for the first time to Aberdeen's level of 42.2. From that time the Aberdeen and Dundee rates behave similarly, both rising markedly, being unlike only in that the Dundee apex is reached in 1911-1915, at 56.7, the rate falling subsequently to 51.5 in 1921-1925, while the Aberdeen rise continues until 1916-1920 to 53.5, and there is practically no fall in 1921-1925. The Edinburgh and Glasgow rates show less variation from 1901-05 to 1916-20, although Edinburgh rises 5 points in the fifteen years, and both towns exhibit a distinct improvement in the 1921-1925 quinquenniad, Edinburgh falling from 44.1 to 37.0, and Glasgow from 41.7 to 37.6.

Table 1A and Chart 1A are complementary to Table I and Chart I. Table I and Chart I show the rates of infant mortality from the developmental group of the four towns; Table 1A and Chart 1A deal with the values of  $\frac{x-\bar{x}}{\sigma x}$  where

$x$  = the value of the variate, the infant mortality from the developmental group per 1,000 live births for any period;

$\bar{x}$  = the mean value of  $x$ ;

$\sigma x$  = the standard deviation of the distribution of  $x$ .

The expression  $\frac{x-\bar{x}}{\sigma x}$  therefore shows the deviation of the infant mortality for each period, compared with its own variability as measured by the standard deviation. Distributions of infant mortality per 1,000 births for the various towns can thus be compared, as they are all reduced to a common standard deviation of unity.

TABLE 1A.  
VALUES OF  $\frac{x-\bar{x}}{\sigma x}$ . FOUR PRINCIPAL SCOTTISH TOWNS (1856-1925).

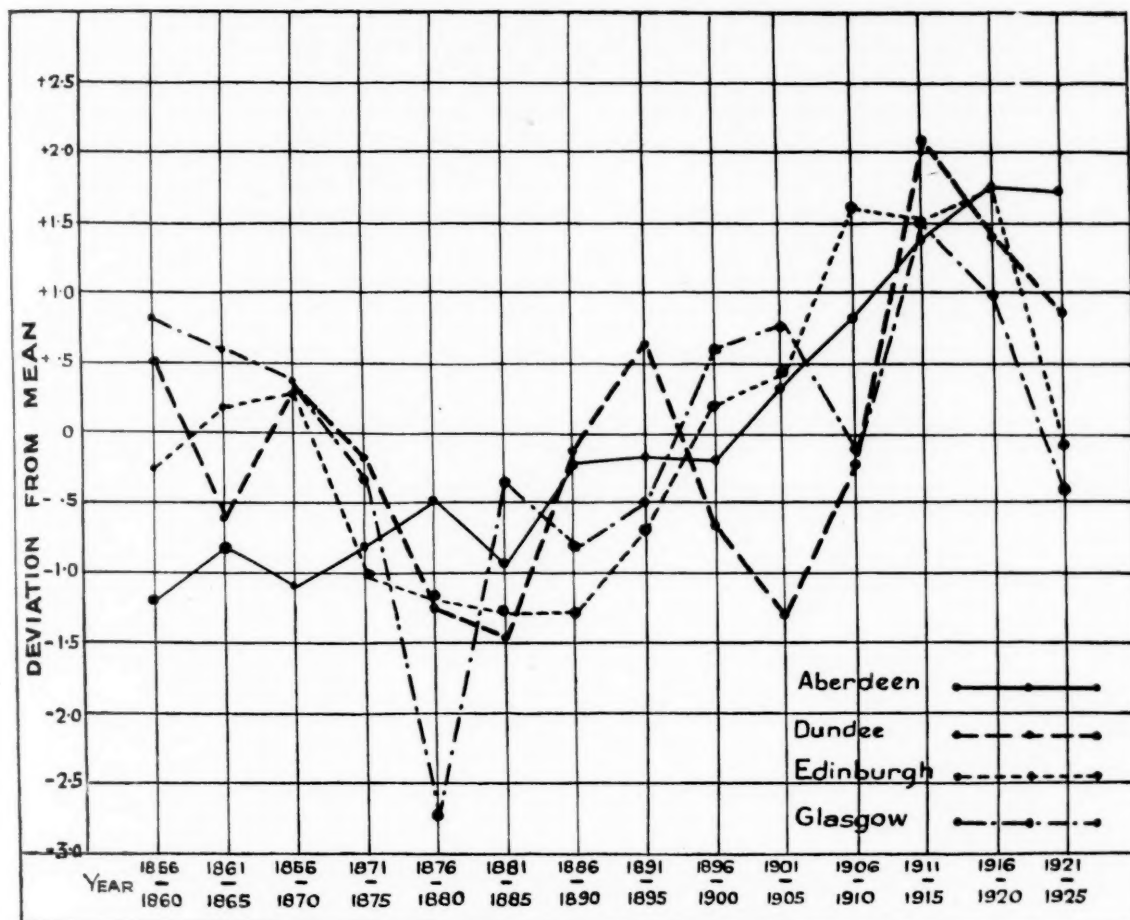
YEAR. Mean of :	ABERDEEN.		DUNDEE.		EDINBURGH.		GLASGOW.	
	$x$	$\frac{x-\bar{x}}{\sigma x}$	$x$	$\frac{x-\bar{x}}{\sigma x}$	$x$	$\frac{x-\bar{x}}{\sigma x}$	$x$	$\frac{x-\bar{x}}{\sigma x}$
1856-1860 ...	29.6	-1.17	50.0	.51	36.5	-.23	41.2	.79
1861-1865 ...	32.3	-.84	45.3	-.58	38.1	.18	40.6	.59
1866-1870 ...	30.2	-1.10	49.1	.30	38.5	.28	39.9	.36
1871-1875 ...	32.5	-.82	47.0	-.19	33.3	-1.05	37.7	-.36
1876-1880 ...	35.3	-.48	42.4	-1.26	32.7	-1.21	30.5	-2.73
1881-1885 ...	31.3	-.96	41.5	-1.47	32.3	-1.31	37.7	-.36
1886-1890 ...	37.4	-.22	47.2	-.14	32.3	-1.31	36.3	-.82
1891-1895 ...	37.7	-.18	50.6	.65	34.8	-.67	37.2	-.53
1896-1900 ...	37.5	-.21	45.0	-.65	38.3	.23	40.6	.59
1901-1905 ...	42.1	.35	42.2	-1.30	39.0	.41	41.0	.72
1906-1910 ...	45.9	.82	46.7	-.26	43.6	1.59	38.4	-.13
1911-1915 ...	50.8	1.42	56.7	2.07	43.3	1.51	43.4	1.51
1916-1920 ...	53.5	1.75	53.8	1.40	44.1	1.72	41.7	.95
1921-1925 ...	53.2	1.71	51.5	.86	37.0	-.10	37.6	-.39
	$\bar{x}=39.2$	$\sigma=8.19$	$\bar{x}=47.8$	$\sigma=4.3$	$\bar{x}=37.4$	$\sigma=3.98$	$\bar{x}=38.8$	$\sigma=3.04$

$x$  = infant mortality from group of developmental diseases.

$\bar{x}$  = mean of  $x$ .

$\sigma x$  = standard deviation of  $x$ .

CHART 1A.

VALUES OF  $\frac{x - \bar{x}}{\sigma x}$ . FOUR PRINCIPAL SCOTTISH TOWNS (1856-1925). $x$  = infant mortality from group of developmental diseases. $\bar{x}$  = mean of  $x$ . $\sigma x$  = standard deviation of  $x$ .

It is seen that Aberdeen exhibits the greatest variability, for while there is little difference in the means of Aberdeen, Edinburgh, and Glasgow, the figures being 39.2, 37.4 and 38.8 respectively, the standard deviations are 8.19 for Aberdeen, 3.98 for Edinburgh, and 3.04 for Glasgow. Dundee has a mean of 47.8 with a standard deviation of 4.3.

The steady and almost continuous rise of the Aberdeen rate is accentuated in this chart. Thus its values for 1856-1900 are all negative (*i.e.* below the mean) from -1.17 in 1856-1860 to -2.1 in 1896-1900, and from 1901-1925, its values are all positive (*i.e.* above the mean) and increase steadily in amount, reaching 1.71 in 1921-1925. Dundee and Glasgow start above their respective means in 1856-1860, Dundee with a value of .51, and Glasgow with a value

of .79. Edinburgh sets off with a negative value  $-.23$ , but by 1866-1870 there is little difference between the three towns, Dundee being at .3, Edinburgh .28, and Glasgow .36. The corresponding figure for Aberdeen is  $-1.1$ . The following 30-35 years mark a period of low values for Dundee, Edinburgh and Glasgow. All fall considerably below their means, but Glasgow reaches its lowest point in 1876-1880 at  $-2.73$ , Dundee's lowest value is  $-1.47$  in 1881-1885, five years later, while Edinburgh continues to fall until 1886-1890 when its value is  $-1.31$ . At this period the Aberdeen value has reached  $-.18$ . All four towns now enter on a period of increasing values, and the resemblance between the experience of each town is marked (which was less obvious in the graph of the actual death rates), although Dundee shows a fall to  $-1.3$  in 1901-1905, which is not repeated in the other three towns. Glasgow, again, falls to  $-.13$  in 1906-1910, after a value of .72 in 1901-1905. The rate of increase in all four towns is such that in 1911-1915 Aberdeen = 1.42, Dundee = 2.07, Edinburgh = 1.51, and Glasgow = 1.51. For Dundee and Glasgow this represents their highest point, and by 1916-1920 Dundee has fallen to 1.4, and Glasgow to .95. Aberdeen and Edinburgh continue to rise to their respective maxima in 1916-1920, 1.75 for Aberdeen, and 1.72 for Edinburgh. In the final quinquenniad, 1921-1925, Edinburgh follows the lead of Dundee and Glasgow in a rapid fall, the values being .86 for Dundee,  $-.10$  for Edinburgh, and  $-.39$ , for Glasgow, and Aberdeen is left in an isolated position 1.71 above its mean.

The exact significance is doubtful, but it is clear that the early advantage which Aberdeen exhibited over the other three Scottish towns in regard to infant mortality has been lost largely by reason of the alarming increase in mortality from developmental diseases shown by Aberdeen, against the almost stationary or even decreasing rate of the other towns.

It may be suggested that Aberdeen's increase may be partly due to a change in nomenclature whereby deaths formerly classified 'from unknown or ill-defined causes' are now included in the developmental group, but as this increase is not evident to the same extent in the other three towns, such a suggestion implies that the Aberdeen practitioner is an isolated product in the matter of improved diagnosis of developmental errors, a conclusion which is hardly justified.

In order to afford a rough test of the extent to which the increase in 'developmental' deaths in Aberdeen is an apparent one, due to changes in classification I have calculated (Table IIA) for four random years throughout the period (1) the percentage of developmental deaths which occur under 3 months; this is found to be 90-93 per cent. until 1901, while in 1921 it has fallen to 81 per cent.; (2) the percentage distribution of the 0-3 months deaths due to developmental diseases, bronchitis and pneumonia, digestive diseases, convulsions, and other causes. Again, the percentage due to developmental diseases remains fairly constant, about 50 per cent. until 1901, and the decrease in the percentage of deaths from 'other causes' from 23 per cent. in 1867 to 17 per cent. in 1901, appears to be reflected more in the rates from bronchitis

and pneumonia, digestive diseases and convulsions, all of which claim a larger share. In 1921, the percentage due to developmental diseases has risen to 66 of the total 0-3 months deaths, while the percentage of 'other causes' has fallen from 17 to 11, bronchitis and pneumonia from 11 to 9, digestive diseases from 10 to 7, and convulsions from 10 to 7. This suggests a transference to some extent, but it must be remembered that the total 0-3 months mortality has fallen during this period, and the natural result would be a higher proportion of deaths from the cause least amenable to post-natal preventive measures.

TABLES IIA AND IIB.

	1867		1883		1901		1921	
(A)	Aberdeen.		Aberdeen.		Aberdeen.		Aberdeen.	
% of Developmental Deaths which occurred from 0-3 months ...	93		90		93		81	
% of Deaths under 3 months due to:—								
Developmental Group ...	53		47		52		66	
Bronchitis and Pneumonia ...	9		12		11		9	
Digestive Diseases... ..	8		12		10		7	
Convulsions ... ..	8		11		10		7	
Other ... ..	23		18		17		11	
(B)	Aberdeen.	Glasgow.	Aberdeen.	Glasgow.	Aberdeen.	Glasgow.	Aberdeen.	Glasgow.
% of Developmental Deaths which occur from 0-3 months ...	93	88	90	89	93	91	81	88
% of 0-3 month Deaths due to Developmental Group ...	53	51	47	53	52	54	66	63
% of infant deaths due to Unspecified causes ... ..	0	4	1	1	1	2	0	4

- (A) Proportion of Developmental deaths which occur under 3 months, and  
Proportion of deaths under 3 months due to various causes. } Aberdeen, 1867, 1883, 1901, 1921.
- (B) Proportion of Developmental deaths which occur under 3 months, proportion of 0-3 months deaths due to Developmental group, and proportion of infant deaths due to unspecified causes, Aberdeen, and Glasgow, 1867, 1883, 1901, 1921.

A comparison between Aberdeen and Glasgow on similar lines (Table IIB) giving, (1) percentage of developmental deaths occurring under 3 months; (2) percentage of 0-3 months deaths due to developmental diseases; (3) percentage of total infant deaths due to unspecified causes, shows that until 1901 there was very little difference between the two towns. In 1921 the

percentages of the total deaths under 3 months due to developmental causes still correspond in the two towns, but the Glasgow percentage of developmental deaths which occur under 3 months has decreased only from 91 to 88, while the Aberdeen percentage has decreased from 93 to 81. The percentage of infant deaths due to unspecified causes is not large enough in either town to be of any moment.

The evidence afforded does not support the suggestion that the increase in the Aberdeen infant mortality from developmental causes is more apparent than real. The most that can be said is that in Aberdeen in the last twenty years a larger proportion of deaths occurring over 3 months are certified as developmental than is the case in Glasgow. This may mean either that a larger proportion of such children survive the 3 months age period in Aberdeen, or that there is a certain amount of difference of certification in the two towns.

## II. RACIAL COMPOSITION OF TOWNS.

Certain facts relative to the influence of heredity seem worthy of discussion. We have seen that, over the seventy years studied, the environmental conditions of the four principal Scottish towns are at their worst in Glasgow, and at their best in Aberdeen: moreover, the period during which Glasgow was the only town of the four able to show a decrease in infant mortality was the very period at which it was undoubtedly 'the unhealthiest town in Scotland.' Huntington<sup>2</sup> writes:—

The geographer and ecologist insist that history must be interpreted in terms of environment, the historian insists that it must be interpreted in terms of events and personalities, the anthropologist insists on an interpretation in terms of races. All are right, for what is needed is a synthesis of the various points of view. The character of any race is a function partly of the present environment, and partly of countless past environments which have selected first one type and then another for preservation, and thus have played a large part in moulding racial character.

### (a) *Influence of racial variation on infant mortality.*

The influence of change in the racial composition of the population of the city of New York, due to the large stream of immigration, on the infant mortality, has been studied by Meyer<sup>3</sup>. The infant mortality for the year 1915, including all races, was 98.2. For children of American parents it was 106.3, for Italians 103.2, for Austro-Hungarians 79.8, and for Russian Poles 77.9. The last two are almost entirely Jews. Guilfoyl<sup>4</sup> produces a table of infant mortality from congenital diseases, grouped according to the nationality of the mother, for the Borough of Manhattan, in the year 1915. Each group deals with from 9,000–17,000 births, and the rates are 54.4 per 1,000 births where the mother is American, 32.0 in the case of Russian parentage, 28.4 for Austro-Hungarians, and 29.5 for Italians. Meyer<sup>3</sup> found that the influence of the racial factor was most marked in the groups of diarrhoeal and congenital diseases. He remarked that Russians, Poles, Austrians, and Italians had entered America in increasing numbers from year to year, especially since 1900,

and he decided that the increase in the foreign element of the city had tended to accelerate the rate of decline of the infant mortality rate. Little<sup>5</sup> publishes an interesting study from records (including still-births) of a lying-in hospital in New York. The types of mating included (1) those within each of the following nationalities, English, Irish, Scottish, Italian, Russian, Greek, Austrian, and German, (2) all possible first generation matings between members of these nationalities. The results give a markedly higher ratio of male births in the hybrid stock, and a separate examination of the still-birth data indicated that they were more frequent in the pure races than in the crosses. As the latter fact was tested only for first generation matings Little suggests that the lower frequency of still-births in the crosses was probably a result of hybrid vigour. In the census report (1871) for Scotland<sup>6</sup> it was noted that emigration increased the fertility of women for the first generation.

In De Porte's<sup>7</sup> study of inter-racial variation in infant mortality he decided that 'the racial groups whose infants suffer more from environmental defects, suffer less from causes that are mainly dependent upon the child-bearing mechanism of the mother. Economic and social conditions have little effect upon this period of infant mortality. Here nature plays no favourites, and non-viable and malformed infants are equally frequent among the rich and the poor.' Forbes<sup>8</sup>, dealing with the statistics of Brighton from 1901-1920, commented on the fact that there was very little difference in the 0-1 month death rate in the different social groupings. On the other hand, Chalmers'<sup>9</sup> inquiry in Glasgow, representing the average experience of the three years 1909-1912, suggested a grading of the immaturity death rates in correspondence with the general death rate, *i.e.*, they were higher in the poorer districts.

(b) *Changes in racial composition of the four principal Scottish towns from 1871.*

The 1871 census report contains a discussion on the races of men in Scotland which has sufficient relevance to deserve full quotation.

Some knowledge of the races of men who inhabit a country has always been deemed of importance when considering the statistics of its population. The lowlands are inhabited by that mixed race to which the term Anglo-Saxon is now generally applied. This is an energetic race, sprung from a mixture of all the various nations which have invaded the country and settled among its original inhabitants, the Goths, Romans, Gauls or Celts, Saxons, Danes, Normans, and Norsemen from Norway and Sweden.

The whole of the highland portion has as its leading inhabitants a nearly pure Celtic race still retaining their ancient language and showing in their configuration and general character the peculiarities of that race.

A race, however, of nearly pure Norsemen, originally from Norway and Sweden, now constitute the majority of the inhabitants of Orkney and Shetland, of the county of Caithness, and of a great many of the fishing villages on the northern and eastern coasts of Scotland, even down to the fishing villages of Buckie, and Newhaven in the Firth of Forth.

Till the year 1820 these were the three races of men in Scotland, but during that year an invasion or immigration of the Irish race began, which slowly increased till it attained enormous dimensions after 1840. This invasion of the Irish is likely to produce far more serious effects on the population of Scotland than even the invasions of warlike hordes of Saxons, Danes, or Norsemen. Already in many of our towns do the persons born in Ireland constitute from

5-15 per cent. of the population; and if we include their children, born in this country, from 10-30 per cent. of the population of these towns consists of the Irish Celtic race. The immigration of such a body of labourers of the lowest class, with scarcely any education, cannot but have most prejudicial effects on the population. As yet the great body of these Irish do not seem to have improved by their residence among us; and it is quite certain that the native Scot who has associated with them has most certainly deteriorated. It is painful to contemplate what may be the ultimate effect of this Irish immigration on the morals and habits of the people and on the future prospects of the country."

In the same report (1871) it is noted that while Shetland is the worst housed county in Scotland, 90 per cent. of her population living in houses of one or two rooms with or without windows, 'so many crude and unsupported theories are now brought forward and proclaimed as facts that it seems right to mention that she stands pre-eminent for the healthiness of her population, and also for their morality; which leads us to conclude that house accommodation is only one of the causes, and after all perhaps not one of the most important, which affects the healthiness and morality of a people.'

Table III, prepared from the census reports, shows the proportion of Scottish, Irish and Foreign born, in the populations of Aberdeen, Dundee, Edinburgh and Glasgow from 1871-1921. It will be noted that the Aberdeen population is the purest race of the four, 95 per cent. of her population being Scottish born; Glasgow is the most hybrid, only 83 per cent. of her population in 1881 being Scottish born, although by 1921 the percentage has risen to 88: Dundee and Edinburgh are intermediate, Edinburgh being the more hybrid of the two, with an average percentage of 90 Scottish born; Dundee had 89 per cent. of Scottish born in her population in 1881, but the rate of immigration decreased at the beginning of the century, and in 1921, 95 per cent. of the population was Scottish born. The largest non-Scottish element was due to the Irish 'invasion' commented on so unfavourably in the 1871 census report. In Glasgow the proportion of Irish born was as high as 14 per cent. in 1871, compared with 11 per cent. in Dundee, 4 per cent. in Edinburgh, and .9 per cent. in Aberdeen. The rate of Irish immigration was continued to a greater extent in Glasgow than in the other three towns. In 1921, the percentage of Irish born in Glasgow was 6.4, in Edinburgh it was only 1.5, in Dundee 1.4, and in Aberdeen .3.

In regard to the foreign population, apart from the Irish, Glasgow has again the highest proportion, Edinburgh comes second and Dundee and Aberdeen have never more than .2-.4 per cent. The Glasgow percentage varies from two to five times the Aberdeen percentage.

When the children of the foreign population, born in Scotland, are included, the percentage of foreign stock (including Irish) in Glasgow is seen to be very great. Tocher<sup>10</sup> found that in 1901, 42 per cent. of the total number of foreigners in Scotland resided in Glasgow alone, and that the most densely populated part of the city contained a larger proportion of foreigners than the less densely populated parts; in fact that the foreign element resided largely in the districts of one- and two-roomed houses. Levy<sup>11</sup> commented on the fact

that the lowest still-birth and neo-natal mortality rates were found in foreign mothers whose economic social and housing conditions would naturally be held to be unfavourable.

An additional point of interest in Tocher's survey is that the foreigners in Glasgow are mostly Jews, 60 per cent. Russian and Polish, and 15 per cent. Italian. The Jewish infant mortality is known to be low. Hertz<sup>12</sup> states that it is only half that of the general population, and among the poorer class Jews even less. He mentions two factors which may contribute to this low mortality, (1) the mothers invariably nurse their children, (2) the total absence of alcoholism among Jewish women. The disfavour with which the Rabbis regard marriage of the physically unfit, or of those with a family history of transmissible disease may be an even more potent factor.

TABLE III.

PROPORTION OF SCOTTISH, IRISH AND FOREIGN-BORN IN POPULATIONS OF FOUR PRINCIPAL SCOTTISH TOWNS, 1871-1921.

Year.	Aberdeen.				Dundee.				Edinburgh.				Glasgow.			
	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>
1871	88	—	·9	—	120	—	11	—	201	—	4	—	478	—	14	—
1881	105	96	·7	·2	142	89	8	·2	234	89	4	·4	511	83	13	·4
1891	122	95	·5	·2	155	91	5	·2	261	91	3	·4	566	85	10	·4
1901	154	95	·4	·2	163	93	3	·2	317	90	2	·6	776	85	9	1
1911	164	95	·3	·3	165	94	2	·3	320	90	1·6	·7	784	88	6·7	1
1921	159	95	·3	·3	168	95	1·4	·4	420	89	1·5	·7	1034	88	6·4	·9

*a* = population in thousands.

*b* = percentage of Scottish born.

*c* = percentage of Irish born.

*d* = percentage of Foreign born.

Brownlee<sup>13</sup> finds that a free mating population becomes stable on a Mendelian hypothesis, in one generation, but that differences of religion check intermarriage, and where Roman Catholics and Protestants inhabit the same valley they keep themselves more or less apart, and slightly different types develop within the same region. Towns also afford an exception and he states that immigration into these has been so marked in the last sixty years (before 1911) that there is not yet time for the production of a homogenous race mixture, and in these centres especially, religion has proved a bar to free intermarriage.

One marked difference has therefore been discovered between the constitution of the Glasgow population and that of the other three principal Scottish towns. Glasgow contains a much larger proportion of Irish and Jews, both of which races are known to have a low infant mortality, than exists in any other town in Scotland. The evidence submitted from towns where analyses of the effect of a foreign element in the population have been made, suggests that immigrating stock adds vigour to the native stock, and that a lowered infant mortality results, the deaths from developmental diseases being the group which is mainly affected. The data are insufficient to prove the exact effect

of immigration on the Glasgow infant mortality. It would be curious if the increasing number of Irish in Glasgow, which has been so much deplored, should be found to have accelerated the decrease in infant mortality, which has been deemed a matter for congratulation.

The English Registrar-General's note in his Statistical Review<sup>14</sup> that the mortality from premature births varies much more with the geographical section of the country than with the degree of urbanization, is worth recording. Taking the country as a whole the excess of North over South is 29 per cent., but that for the county boroughs over the rural districts is 13 per cent. My findings do not lead me to agree with his conclusion that 'these facts would seem to accentuate the possibility of further reduction in the neo-natal mortality, as it should be more feasible to approximate the conditions of foetal and infant life in the North to these prevailing in the South, than to overcome for the great towns their disadvantages as compared with the rural districts.' The very fact that the infant mortality from this cause varies more with the geographical section of the country than with the degree of urbanization suggests that urbanization is not the dominant factor in producing this mortality.

It has been found that while Aberdeen has been ahead of the other three principal Scottish towns in housing and sanitary reform, and has never suffered the same degree of congestion as Glasgow and Dundee, nevertheless the rate of decrease of infant mortality in Aberdeen has been considerably less than in any of the other three towns. Further, if the mortality rates from separate causes are to be regarded as having any significance, it is to the group of developmental diseases that we must look for a solution of the problem.

(c) *Comparison of Mortality rates from the Group of Developmental Diseases in the County of Aberdeen, and in the Town of Aberdeen, 1856-1925.*

The fact that 95 per cent. of the population of Aberdeen is Scottish, and that 75 per cent. are born in Aberdeenshire, led me to investigate the infant mortality from the developmental group in the County of Aberdeen.

In the reports of the Registrar General (Scotland), mortality figures for counties are distributed either according to age or according to disease, but not for the two simultaneously. Accordingly, it was not possible to obtain the absolute number of deaths under one year from the developmental group in the County of Aberdeen. Deaths certified as due to congenital malformations, prematurity or atelectasis, may safely be taken as occurring under one year, but in the case of deaths from atrophy or debility, a number occur in the second year, or even later. To obtain a fair estimate I referred in each year to the deaths from these causes in the town of Aberdeen, noted what proportion occurred under one year and allowed a similar proportion in calculating the death rate of the developmental group, in the county. The figure is as accurate as can be obtained under the circumstances, and reference to Table IV shows how closely it follows the trend of the mortality from the same causes in the

TABLE IV.

INFANT MORTALITY FROM GROUP OF DEVELOPMENTAL DISEASES :  
COUNTY OF ABERDEEN AND TOWN OF ABERDEEN (1856-1925).

Year. Mean of :	COUNTY OF ABERDEEN.			TOWN OF ABERDEEN.		
	No. of births.	Development group.		No. of births.	Development group.	
		No. of deaths.	Infant Mortality.		No. of deaths.	Infant Mortality.
1856-1860	4,818	89	18.4	2,397	71	29.6
1861-1865	5,095	100	19.6	2,663	86	32.3
1866-1870	5,248	108	20.6	3,010	91	30.2
1871-1875	52,27	131	25.0	3,169	103	32.5
1876-1880	5,434	149	27.4	3,480	123	35.3
1881-1885	5,222	110	21.0	3,712	116	31.3
1886-1890	4,960	131	26.4	3,827	143	37.4
1891-1895	5,293	143	27.0	4,114	155	37.7
1896-1900	4,473	136	30.4	4,636	174	37.5
1901-1905	4,046	134	33.1	4,872	205	42.1
1906-1910	3,877	123	31.7	4,505	207	45.9
*1911-1915	3,512	136	38.7	3,959	201	50.8
1916-1920	3,066	116	37.8	3,479	188	53.5
1921-1925	3,271	129	39.4	3,763	201	53.2

\* Corrected for transfers from 1911.

town of Aberdeen. The county rate has risen from 18.4 in 1856-1860 to 39.4 in 1921-1925, an increase of practically 90 per cent. The parallel fall in town and county rates in the 1881-1885 period, and the subsequent rise in both is striking. The correspondence in more recent years is less marked, but there is a sufficient degree of resemblance to suggest a defect common to the two populations. What is the nature of the defect must be a matter for speculation until the data necessary for its solution are extended and elaborated.

The hypothesis that Aberdeen (both town and county) is breeding to an increasing extent from that portion of her population which suffers from developmental defects, must be considered.

### III. SUMMARY AND CONCLUSIONS.

*Group of Developmental Diseases.*—Examination of the infant mortality from the group of developmental diseases in the four principal Scottish towns from 1856-1926 shows that the mortality from this cause has increased by 79 per cent. in Aberdeen, by 3 per cent. in Edinburgh, and by 1 per cent. in Dundee, while the Glasgow mortality has decreased by 9 per cent. It seems clear that the early advantage which Aberdeen exhibited over the other three Scottish towns in regard to infant mortality has been lost largely by reason of its alarming increase in mortality from developmental diseases. As far as can be judged the increase is real rather than apparent.

*The Racial Factor and Infant Mortality.*—Meyer decided that the increase in the foreign element in the New York population had tended to accelerate the rate of decline of infant mortality, and other observers have noted the increased vigour of hybrid stock, with a diminution in infant mortality affecting particularly the deaths from developmental diseases.

No data are available to prove the effect of this racial factor on the Scottish infant mortality statistics, but it is notable that the town which has shown the steadiest rate of decrease in infant mortality, namely Glasgow, is the town of most hybrid stock, and that the town possessing the purest race (Aberdeen) is also the town where there has been least decrease in infant mortality. It is interesting, also, to find that the trend of infant mortality from developmental diseases in the County of Aberdeen, from 1856-1926 shows a striking parallelism with the mortality from the same group in the town of Aberdeen, although at a lower level.

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# STUDY OF ULTRA-VIOLET RADIATION IN THE TREATMENT OF TUBERCULOSIS IN CHILDHOOD.

BY

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| I. INTRODUCTION. (T. HARTLEY MARTIN).   | III. OBSERVATIONS ON ENDOCRINE ACTIVITIES AND CARBOHYDRATE TOLERANCE IN CONNECTION WITH ULTRA-VIOLET RADIATION. (JOHN D. CRAIG). |
| II. THE SEDIMENTATION RATE AND BLOOD PRESSURE AS CRITERIA OF THE VALUE OF ULTRA-VIOLET RADIATION IN TUBERCULOSIS OF CHILDHOOD. (JOHN D. CRAIG). | IV. EXPERIMENTAL DATA AND CONCLUSIONS. (JOHN D. CRAIG).  |

## I. INTRODUCTION.

In an endeavour to explore every avenue for the treatment of non-pulmonary tuberculosis in children a visit was paid to the Finsen Institute in Copenhagen in October, 1921, to gain first hand knowledge of the methods employed at that centre in view of the results claimed.

Although between 80 and 85 per cent. of the cases treated in this hospital by fixation and natural helio-therapy were discharged quiescent, it was felt that artificial light might secure (1) a greater percentage of 'recoveries'; (2) a reduction in the time required to attain 'recovery'; (3) an amelioration in the condition of advanced and complicated cases which had failed to respond to open-air treatment.

The visit to Copenhagen was of too short a duration to confirm with certainty the above-mentioned queries, but it was felt that sufficient evidence had been produced to allow of an experimental installation of artificial light. Two long-flame carbon arc lamps were therefore installed in August, 1922, and the following technique was used:—Routine acclimatization was commenced, 10 minutes (5 back, and 5 front) at 3 feet being the initial dose. This was increased by 10 minutes every other day until a full hour could be given three times a week. Departures from this routine were made in cases where idiosyncrasy to any given doses was shown.

The results achieved over six years have been encouraging. The most marked advantage obtained by artificial heliotherapy has been the ability to

supply regular stimulus by means of organized periodic doses of light, and this has undoubtedly reflected itself upon the local foci of disease because of the marked improvement in the general condition of the children treated.

Although it is as yet too early to say that greater percentage of recoveries has been obtained, and although it has been definitely established that the cases in an advanced stage of disease do not benefit by such treatment but are rather made worse, there is definite evidence to show that the duration of stay in hospital of cases of tuberculous adenitis and tuberculous peritonitis has been lessened, and that fewer of these cases relapse on return to home life than was the case formerly. It was, however, felt that more conclusive evidence as to the value of artificial light treatment should be obtained, and, in order to attempt to secure this, research work was undertaken by Dr. John D. Craig, the details of which are amplified in the accompanying articles.

The results obtained were satisfactory up to a certain point and it is felt that the conclusions warranted a continuance of such research over a longer period and the production of further evidence as a result of experiments of (1) treatment by 'light' in the earliest stages of disease; (2) the reaction to 'light' of varying wave lengths.

## II. THE SEDIMENTATION RATE AND BLOOD PRESSURE AS CRITERIA OF THE VALUE OF ULTRA-VIOLET RADIATION IN TUBERCULOSIS OF CHILDHOOD.

### THE SEDIMENTATION RATE OF ERYTHROCYTES.

In the days when blood letting was common it was a recognised phenomenon that the settling rate of blood corpuscles with the formation of a '*cruor sanguinis*' was increased in inflammatory conditions and this was considered to be an important clinical sign by Hewson (1771) and Hunter (1794).

Probably on account of the decline of blood-letting the test was allowed to become dormant until 1917 when Fohrœus<sup>1</sup> drew attention to it, and again in 1921 when Westergren<sup>2</sup> published an account of his technique and conclusions. Since that time an immense literature has appeared, most of it emanating from Continental centres, but some more recently from America.

In England Heaf<sup>3</sup>, Lyle Cummins and Acland<sup>4</sup>, and R. G. Bannerman<sup>5</sup> have made contributions to the literature.

Most of the work referred to above has been done with a view to using the sedimentation rate as a test in diagnosis, and in this respect it has been disappointing; for, as is shown in the following notes, its value as an aid in diagnosis is limited. In one aspect, however, namely as an aid to prognosis, and particularly as a criterion of the effect of treatment, there is almost unanimous approval that it is of value.

It was during the period when search was being made in the literature for assistance in assessing the value of ultra-violet radiation that attention was drawn to Heaf's<sup>3</sup> work on this test, and further enquiries supported his views. Because of this it was felt that there was justification for further experimentation with this test for the purpose in view.

*Mode of action.* The factors controlling the sedimentation reaction are not yet fully understood. Fohræus demonstrated that in rapidly sedimenting blood there is a relative excess of fibrinogen and globulin as against albumen, and that the auto-agglutination of red blood corpuscles is an essential element, since on physical grounds a clump of red blood corpuscles will fall at a greater speed than discreet cells. Bannerman<sup>5</sup> states that the number of red blood corpuscles has but little influence on the sedimentation rate, which was found in a case of severe anæmia to be within normal limits. Beaumont and Dodds<sup>7</sup> suggest that breaking down of tissue proteins may account for an increased rate of sedimentation.

The suggestion is made that for the purposes of translating the month to month variation of this test the rate of fall is in proportion to the activity of the disease. Thus a rise in the rate of sedimentation, *i.e.*, diminished numerical reading, is taken to mean a temporary increase in the activity in the focus of disease, whereas a fall in the rate, *i.e.*, a higher numerical reading, implies a temporary decline in the activity of the disease.

Westergren gives the following figures for the classes into which observations fall:—

1. Clear fluid column of 3 mm. (197 mm–200 mm.) is normal.
2. „ „ „ „ 4–6 mm. (194 mm.–196 mm.) is doubtful.
3. „ „ „ „ 7–12 mm. (188 mm.–193 mm.) is probably pathological.
4. „ „ „ „ over 12 mm. (under 188 mm.) is certainly pathological.

*Technique.* 0.4 c.cm. of a 3.8 per cent. solution of sodium citrate in sterile distilled water is drawn up into a 2 c.cm. syringe. Slight ligature-pressure, which is necessary in children, is then applied to the upper arm and the patient's median basilic vein punctured. 1.6 c.cm. of blood is withdrawn so that the syringe is now filled with blood and citrate up to the 2 c.cm. mark without any air bubbles intervening. The contents of the syringe are now placed slowly into a small dry gallipot.

A pipette holding 1.25 c.cm. graduated individually into 200 divisions is taken, and drawing up the citrated blood at least five times thoroughly mixes the contents of the gallipot. It is finally sucked up to the 200 mm. mark on the pipette, care being taken to obtain a column of blood without air bubbles. The pipette is placed in a vertical position on a special stand and the reading of the height of the column of red blood corpuscles taken at the end of one hour.

Various investigators have taken readings at hourly intervals for 24 hours, but in this work the one-hour reading has been used as it is generally agreed that for comparative purposes it is the most useful. To verify the results of others, a series of cases were examined at the beginning in which the readings were taken at the first, second, third, fourth, fifth, sixth, ninth, twelfth, eighteenth and twenty-fourth hours. The results agreed within limits with Heaf, and thereafter the one-hour reading was the only one taken.

TABLE I.  
SEDIMENTATION RATES AND BLOOD PRESSURE READINGS IN CASES TREATED BY  
ULTRA-VIOLET RADIATION.

Case No.	Diagnosis.	Stage.	Monthly Readings of Sedimentation Rates and Blood Pressure.	Clinical Progress.
21	Spine ..	C.3.	S.R. 121 135 125 116 92 104 116 B.P. 106 110 94 86 106 102 92	No change.
22	Hip .. ..	C.3.	S.R. 135 113 103 B.P. 114 108 110	Died.
23	Knee ..	C.3.	S.R. 118 128 90 B.P. — — —	Very much worse. U.V.R. stopped.
24	Hip .. ..	C.3.	S.R. 102 106 73 B.P. 111 112 112	Worse. U.V.R. stopped.
25	Hip .. ..	C.3.	S.R. 165 152 136 151 B.P. 114 106 111 116	No change.
26	Hip .. ..	C.3.	S.R. 87 77 110 156 168 178 160 184 B.P. 105 99 95 108 108 120 115 112	Much improved.
27	Hip .. ..	C.3.	S.R. 82 66 80 67 70 70 84 73 B.P. 130 118 118 116 129 128 128 121	Worse.
28	Spine ..	C.2.	S.R. 166 187 190 190 193 196 195 195 B.P. 118 112 125 122 122 120 130 134	Improved.
29	Knee ..	C.2.	S.R. 157 154 136 130 B.P. 134 134 134 134	Worse. U.V.R. stopped.
30	Spine ..	C.2.	S.R. 161 168 145 174 168 173 170 B.P. 92 100 102 104 98 98 100	Improved.
31	Hip .. ..	C.2.	S.R. 184 178 162 173 B.P. 104 106 106 110	No change.
32	Hip .. ..	C.2.	S.R. 182 173 134 150 159 B.P. 112 112 115 114 115	Worse.
33	Spine ..	C.2.	S.R. 187 183 189 188 183 B.P. 122 106 115 116 114	No change.
34	Hip .. ..	C.2.	S.R. 191 190 196 189 196 195 197 B.P. — 96 96 90 101 90 108	Improved.
35	Hip .. ..	C.2.	S.R. 179 163 179 187 184 B.P. 100 106 109 121 112	Improved.
36	Spine ..	C.2.	S.R. 192 188 188 191 191 195 192 196 B.P. 128 128 114 114 120 116 112 124	Improved.
37	Hip .. ..	C.1.	S.R. 170 187 191 195 193 B.P. 105 96 104 110 110	Improved.
38	Knee ..	C.1.	S.R. 190 191 193 193 191 B.P. 101 112 106 105 103	Improved.
39	Spine ..	C.1.	S.R. 189 179 187 190 B.P. — — — —	Slightly improved.

TABLE I.—*continued*

Case No.	Diagnosis.	Stage.	Monthly readings of sedimentation rates and blood pressure.	Clinical progress.
40	Spine ..	C.I.	S.R. 167 155 167 186 188 B.P. 94 98 102 105 112	Improved.
41	Peritonitis ..	—	S.R. 195 172 189 194 196 197 196 196 B.P. 100 92 110 110 118 128 122 122	Improved.
42	Peritonitis ..	—	S.R. 166 170 163 177 190 186 190 190 B.P. 94 92 98 92 100 104 102 106	Improved.
43	Peritonitis ..	—	S.R. 141 142 156 150 140 162 146 B.P. 80 80 88 98 95 96 92	Improved.
44	Peritonitis ..	—	S.R. 188 190 186 191 B.P. 120 116 116 117	Improved.
45	Peritonitis ..	—	S.R. 192 198 198 198 198 B.P. — 80 80 85 86	Improved.
46	Peritonitis ..	—	S.R. 123 187 194 194 194 195 192 B.P. — 85 96 110 108 108 110	Improved.
47	Cervical Adenitis	—	S.R. 188 192 198 197 198 195 196 196 B.P. — 109 106 100 112 108 110 110	Improved.
48	Cervical Adenitis	—	S.R. 196 188 193 195 B.P. 112 114 110 105	Improved.
49	Cervical Adenitis	—	S.R. 194 194 194 194 194 194 194 184 195 B.P. — 86 100 98 100 101 100 102 106	Improved.
50	Cervical Adenitis	—	S.R. 160 155 163 190 170 190 195 193 B.P. 110 98 96 118 108 112 116 116	Improved.
51	Cervical Adenitis	—	S.R. 176 134 170 180 B.P. 112 112 118 118	Improved.
53	Ankle ..	—	S.R. 148 163 180 188 B.P. 130 122 115 135	Improved.
54	Elbow ..	—	S.R. 180 194 195 194 192 192 195 B.P. 110 108 100 120 120 122 122	Improved.
55	Ankle ..	—	S.R. 170 185 188 181 B.P. 104 88 101 110	Improved.
56	Epididymitis	—	S.R. 198 192 196 197 B.P. 128 114 122 113	No change.
57	Scrofuladerma	—	S.R. 189 176 191 191 B.P. — — — —	Improved.
58	Lymphangitis	—	S.R. 191 192 197 194 194 B.P. 90 94 106 108 102	Improved.
59	Scrofuladerma	—	S.R. 196 193 195 196 197 192 195 B.P. — 90 95 94 92 102 95	Improved.
60	Kidney ..	—	S.R. 157 184 185 195 196 196 195 192 B.P. — — — — — — —	Improved.

TABLE II.

SERIES OF CONTROL CASES.

Case No.	Diagnosis.	Stage.	Monthly readings of sedimentation rates and blood pressure.							
			S.R.							
1	Right Hip ...	C.2.	S.R.	193	192	193	193	196	197	
			B.P.	88	108	92	94	90	90	
2	Hip ... ..	C.2.	S.R.	168	160	156	164	157	172	
			B.P.	100	100	106	101	102	110	
3	Hip ... ..	C.2.	S.R.	175	188	190	188	191	181	
			B.P.	108	110	110	112	108	111	
4	Hip ... ..	C.1.	S.R.	196	196	197	190	185	196	
			B.P.	98	104	104	98	105	124	
5	Ankle ...	—	S.R.	153	166	168	183	168	174	
			B.P.	105	110	108	110	107	116	
6	Osteitis ...	—	S.R.	180	178	179	178	179	180	
			B.P.	118	114	116	118	119	122	
7	Spine ...	C.2.	S.R.	196	194	195	195	196	197	
			B.P.	95	90	90	96	98	100	
8	Hip ... ..	C.3.	S.R.	74	73	124	156	178	180	
			B.P.	116	112	116	118	110	112	
9	Osteitis ...	—	S.R.	187	190	187	189	188	186	
			B.P.	100	102	100	90	102	104	
10	Hip ... ..	C.2.	S.R.	181	189	189	190	182	190	
			B.P.	120	124	122	124	120	118	
11	Spine ...	C.3.	S.R.	112	174	177	182	195	189	
			B.P.	110	122	120	128	132	132	
12	Knee ...	C.1.	S.R.	197	195	193	194	190	192	
			B.P.	115	114	106	120	115	120	

TABLE II.—*continued.*

Case No.	Diagnosis.	Stage.	Monthly readings of sedimentation rates and blood pressure.							
13	Ankle ...	—	S.R.	136	146	160	159	170	164	
			B.P.	98	108	102	108	112	107	
14	Osteitis ...	—	S.R.	187	192	191	188			
			B.P.	102	96	96	106			
15	Osteitis ...	—	S.R.	168	168	178	180			
			B.P.	100	108	105	106			
16	Spine ...	C.2.	S.R.	190	193	190	193	193	195	
			B.P.	102	102	92	100	102	108	
17	Hip ...	C.1.	S.R.	197	198	198	197	198		
			B.P.	112	112	114	115	120		
18	Hip ...	C.1.	S.R.	189	194	193	192	187	170	
			B.P.	104	114	108	105	110	114	
19	Spine ...	C.3.	S.R.	160	142	153	151	184	170	
			B.P.	82	102	104	104	112	95	
20	Hip ...	C.2.	S.R.	192	192	193	195	194	197	
			B.P.	100	115	114	112	110	104	
21	Knee ...	C.1.	S.R.	192	191	191	186	192		
			B.P.	128	130	126	128	122		
22	Ankle ...	—	S.R.	169	179	176	170			
			B.P.	102	102	102	104			
23	Elbow ...	—	S.R.	180	189	188	191	190		
			B.P.	108	104	104	108	103		
24	Osteitis ...	—	S.R.	171	160	158	153	165	170	
			B.P.	118	110	110	112	109	110	
25	Hip ...	C.2.	S.R.	164	167	148	172	150		
			B.P.	132	122	124	122	128		

In all, some 469 monthly examinations are recorded in these notes.

*Conclusions.*

1. A series of sedimentation rates has a definite place and value in forming an opinion as to the progress and prognosis of tuberculosis in children.
2. As a diagnostic agent its scope is limited. In this work may be found a few cases of undoubted tuberculosis which have a normal sedimentation rate. An abnormal rate is probably always an indication of disease, not necessarily tuberculosis.
3. It is felt that extremes of temperature may alter the reading to some extent. For this reason the room temperature was noted. The temperature of the room in which the readings were taken was almost always between 55° and 60° F.
4. It is considered that a series of sedimentation rates may be of great value in controlling the dosage and the duration of treatment by ultra-violet radiation.

THE BLOOD PRESSURE.

The instrument used was a desk model Baumanometer. The residual systolic pressure was estimated by finger palpation as it was found that the auscultatory method was not practicable in children.

The readings were taken at rest, between exposures to ultra-violet radiation, and at approximately the same time after a meal.

It is to be admitted that in children there is a certain difficulty about the taking of blood pressure, but it was found that after due consideration had been given to this fact there were certain tendencies which could not be disregarded.

The taking of the blood pressure was at first regarded solely in the rôle of a routine examination, but as the number of readings increased the following impressions were gleaned :—

- (1) That in many cases which were clinically and by the sedimentation rate showing marked improvement, the blood pressure rose in a correspondingly definite fashion. Briefly the tendency in cases showing improvement was for the blood pressure to rise. This was also shown in some of the control cases on ordinary routine open-air treatment.
- (2) That following one month's ultra-violet radiation certain cases show a definite fall in blood pressure, and that this often coincided with the fall in the sedimentation rate reading which was referred to as the 'negative phase.'
- (3) That the variations shown in the blood-pressure readings were more marked in those cases receiving radiation than in the control cases.

### III. OBSERVATIONS ON ENDOCRINE ACTIVITY & CARBOHYDRATE TOLERANCE IN CONNECTION WITH ULTRA-VIOLET RADIATION.

During the period that an investigation was being made into the value of ultra-violet radiation in the treatment of tuberculous children, it was observed that in certain cases the reaction to light suggested the possibility of an association between ultra-violet radiation and the endocrine glands.

The relationship between low blood pressure and pigmentation, in particular, gave rise to the premise that the suprarenal glands play more than a passive part in the action of light on the body.

On the strength of these observations, and also upon certain other evidence gleaned from various sources, it was decided to ascertain what effect, if any, the exhibition of suprarenal extract might have on one of these cases. The first case (and for a time the only case) so treated was that of a boy of fourteen who had been on a frame for four years, during the latter part of which he had been receiving ultra-violet radiation. When suprarenal therapy was begun he was almost *in extremis*: there was widespread œdema up to the axillæ, the hip was discharging from twelve sinuses and the buttock was partially gangrenous, the liver and spleen were much enlarged and the urine was loaded with albumen. There was deep brown pigmentation on the whole body. The Wassermann reaction was negative. The blood pressure was 100 mm. and the sedimentation rate was 119 mm. Ultra-violet radiation had been stopped about a month previously, but was re-started when treatment by suprarenal extract was begun. Some eight months later the boy presented quite a different picture: the pigmentation was no longer excessive, the liver though palpable was now shrunken and the spleen was not palpable. There was a trace of albumen in the urine, the B.P. was 130 mm., and the sedimentation rate 138 mm. Since then the improvement has continued, and the patient is now able to get up though he is still an in-patient in the Hospital.

When it was seen that improvement was taking place in this case, other patients were similarly treated, but unfortunately the results in the series of cases were not so encouraging. Following upon this line of thought it was considered that it might help if the efficiency of these glands could be estimated. No reliable method of estimating this efficiency was found in the literature. As it is known that the suprarenal glands influence carbohydrate metabolism, it was thought that it might be of interest to ascertain the patients' carbohydrate tolerance before and after a period of ultra-violet radiation.

The conclusions and technique are embodied in the following paragraphs.

#### THE ADRENALS AND LIGHT.

The hypothesis enunciated in the introduction, namely, that the adrenal glands play more than a passive part in the treatment of disease by ultra-violet radiation, was based upon certain observations in the cases under investigation, and upon other evidence extracted from the literature.

TABLE III.

CASES TREATED WITH SUPRARENAL AND PARATHYROID EXTRACTS IN CONJUNCTION  
WITH U.V. RADIATION.

Case No.	Diagnosis.	Stage.	Monthly readings of sedimentation rate and blood pressure.												Clinical progress.											
11	Hip .. ..	C.3.	S.R. 119	74	79*	71	99	102	90	101	121	138	B.P. 100	92	105	112	128	125	122	132	130	130	Much improved.			
12	Spine ..	C.3.	S.R. 154*	118	148	170											B.P. 114	102	108	112			Worse.			
13	Spine ..	C.3.	S.R. 123	120	95*	107	106	111	96	93	54			B.P. 92	104	88	112	100	92	104	102	102	No change.			
14	Peritonitis ..	—	S.R. 154	140	101	101*	134	116	102	114			B.P. 96	100	100	106	108	112	108	108			No change .			
15	Hip .. ..	C.3.	S.R. 132	107	145	141	142*	130	159	182	168			B.P. 108	110	122	126	126	122	120	126	124	Improved.			
16	Osteitis ..	C.3.	S.R. 148	79	83*	100	110	100	90	98	76			B.P. 84	75	80	92	94	92	95			No change			
17	Hip .. ..	C.3.	S.R. 133	85	117	75	91*	118	81	61			B.P. —	94	108	90	96	104	114	116			No change.			
18	Hip .. ..	C.3.	S.R. 124	122	120*	141	133	130	136	131			B.P. 126	118	110	102	108	116	122	122			Improved.			
19	Spine ..	C.3.	S.R. 94	85*	78			B.P. 102	107	115														Worse.		
20	Peritonitis ..	—	S.R. 178	173	155*	172	188	180					B.P. 92	90	96	112	110	108					Improved.			

\* Denotes beginning of endocrine therapy.

It is suggested that it may be accepted that the visible reaction to light is in the form of a protective pigmentation, and that in suprarenal deficiency there is also present in most cases a pigmentation, although as far as is understood at present there is no evidence to show that these pigments are of an exactly similar nature. The original observation which gave rise to the hypothesis was that certain cases were deeply pigmented, although the disease was progressive, and in many cases the patients were in danger of developing amyloid disease if they had not already done so.

That pigmentation of itself is no criterion in prognosis is shown, by the following extracts :—

(a) Rost<sup>8</sup> and others believe that pigmentation is an undesirable element formed by light radiation in the treatment of tuberculosis.

(b) Mayer<sup>9</sup> states that the sudden development in patients of the capacity to produce pigment may often be associated with the rapid cure of a new tuberculous focus, strongly in contrast with the previous slow healing of an area of disease when the patient did not pigment. Yet frequently patients who have developed marked pigmentation fail to heal their disease.

It was found on further investigation that this particular type of case, the progressive, pigmented and often amyloid patient, had in most instances although not in all, a comparatively low blood pressure. (The question of raised blood pressure with albuminuria is also to be considered in these cases, the majority of which had albuminuria.)

Perhaps a much more significant factor was the initial fall in blood pressure following the first period (one month) of artificial radiation, and that this was often accompanied by a corresponding fall in the sedimentation-rate reading. When this was compared with the fact that in those cases which were showing improvement, the blood pressure tended to rise after the first month, it was wondered whether that secretion in the body best known to be capable of raising blood pressure was associated with these changes.

It has been observed by Mayer and Bell Ferguson<sup>12</sup> that the immediate effect of a light bath is to produce a lowering of the blood pressure, which effect normally disappears within a short time after exposure. This may be explained by a vaso-dilatation of the surface capillaries, and to what extent the sympathetic nervous system could in itself be associated with any of the observations recorded in these notes it would be difficult to say.

In 'sunstroke,' which corresponds to an overdose of sunlight, it is found that the blood pressure remains low. There would appear to be a similarity between sunstroke and surgical shock, and in the latter Crile strongly advocates the use of adrenalin. Dale and Richards<sup>13</sup> have shown recently that adrenalin is able to act directly without being dependent upon other substances, *e.g.*, histamine.

The thought which presents itself is whether the action of adrenalin is that of supplying a physiological want.

Another condition which simulates surgical shock is death in an animal following an injection of hæmatoporphyrin. Gilchrist<sup>14</sup> has stated that investigations into hæmatoporphyrinuria has revealed that the cause of death was the depression of blood pressure and dilatation of vessels. That there is in cases of hæmatoporphyrinuria an extreme 'light sensitiveness' has been shown by Ashby<sup>20</sup> in describing a patient who suffered from attacks of Hydroa whenever the weather was hot and sunny and who was very pigmented and sunburnt. Betz<sup>15</sup> injected into himself 0.2 grm. hæmatoporphyrin and became extremely sensitive to light. Here may be mentioned a case (No. 20) in this series where following two periods of exposure to ultra-violet radiation, with a week's rest in between, there developed on each occasion an erythematous scaly eruption, which disappeared and did not return following the exhibition

of suprarenal extract, the exposure being continued at the same time. Is it reasonable to suggest that in adrenalin may possibly be found a desensitizing agent?

The following paragraph is from Bell Ferguson's book on the Quartz lamp<sup>16</sup> :—

Dr. F. Talbot, in a letter to the *British Medical Journal*, relates how an asthmatical boy was given an ultra-violet radiation bath, and also his brother who was not asthmatical. Within some hours the first mentioned developed an attack of asthma and showed a much milder erythema than his brother. He was given adrenalin. Within half an hour the asthma passed off and 3½ hours later it was observed that his erythema had increased and was now almost as marked as in the case of his brother. Dr. Talbot suggests that the skin's reaction to light makes a demand on the adrenals which in this case temporarily exhausted them and induced an attack of asthma, and that the dose of adrenalin restored the balance and enabled the skin reaction to be completed.

Another aspect of the hypothesis is that of the 'antitoxic' property of the suprarenal capsules which has been suggested by Schafer<sup>11</sup>. He states that enlargement of the suprarenal capsules, mainly of the cortex, has been frequently noticed in infection and as the result of inoculation with disease toxins. As all cases which were treated with suprarenal extract were complicated by a secondary pyogenic infection, the question arises whether the improvement, if any, could be due to some antitoxic action of the suprarenal extract. But if this is true the fact remains that these cases do badly on artificial light and that this might be due to some further adrenal drain.

The addition of parathyroid extract, although empirical, was considered advisable for the following reasons :—

(1) It has been suggested that endocrine extracts have a greater action in combination with one another, and that the parathyroid gland is the complement of the suprarenal gland<sup>17</sup>.

(2) It is known that following a long fixation on frames decalcification occurs, and that this takes place in the neighbourhood of a tuberculous joint. It was considered that the addition of parathyroid extract might assist in mobilizing the calcium content of the body and also in counteracting infection.

(3) Richter<sup>18</sup> suggests that in Addison's disease there is an increased breaking down of bone.

(4) Rabbits exposed to ultra-violet radiation develop a hypertrophy of the parathyroid glands<sup>19</sup>.

It was felt that the injection of adrenalin into the skin was not justified. For that reason and also that perhaps the whole gland would be more likely to produce an action, the dessicated adrenal substance (grn. 2 in gelatine capsules) was used throughout with parathyroid tablets, grn.  $\frac{1}{20}$  (Messrs. Parke, Davis & Co.).

*Conclusions.*

(1) That there has been a therapeutic action in a few cases following the exhibition of these extracts is supported by the following evidence:—

(a) It would appear that the blood pressure has been raised appreciably in some of the cases. (Leyton<sup>21</sup> states that adrenal extract, although when administered by mouth it fails ordinarily to produce elevation of blood pressure, will bring about this effect in cases of Addison's disease.) Two control cases did not show any decided rise following a course—two months—of suprarenal extract.

(b) That the pigmentation in some cases has decidedly diminished in degree following treatment on these lines. (Allowance is made for the fact that some of these cases began treatment in the summer.)

(2) It is too early to weigh up how much improvement has been shown, but when it is remembered that these cases were advanced, and that some of them had entered that last stage which usually terminates in death, it is felt that there has been a definite response in the way desired.

(3) No conclusion regarding the influence of ultra-violet radiation upon the action of the extracts has been made, but it would appear that any change has been independent of the former.

(4) The observations although inconclusive would, it is thought, repay further investigation. It is felt that the particular fields in which trial might be made are: (a) Cases verging on amyloid disease; (b) Cases sensitive to ultra-violet radiation.

## ULTRA-VIOLET RADIATION AND CARBOHYDRATE METABOLISM.

Interest in the adrenal glands having been aroused the question of whether it were possible to estimate their efficiency presented itself. There appears to be no satisfactory method of doing this.

Sergeant<sup>22</sup> has described the appearance of a white line, *la ligne blanche surrénale*, following the stroking of the skin in a case of adrenal insufficiency. This was tried and although it was produced in some of the cases suspected of being deficient in adrenal secretion, it was to an almost equal extent present in many other cases.

It has been shown<sup>23</sup> that an injection of adrenalin produces an increase in the blood sugar and that in Addison's disease the sugar tolerance is increased.

It was felt that it might be of interest to see what effect, if any, a series of exposures to ultra-violet radiation would have on the carbohydrate tolerance. It was thought that, if it were true that light stimulated the formation of, and in some way used up the adrenal secretion, a change might be found in the

sugar-tolerance curves before and after a course of exposures. It was assumed also that any results could not be conclusive, for a stimulus applied to the adrenals probably affects the complete endocrine system, and that any change could be associated with other hormones, as for example, the thyroid or pancreas.

Here may be mentioned the case of an adult female to whom it was suggested by an outside practitioner that a course of ultra-violet radiation might be of benefit to her. The diagnosis was that of nervous breakdown, but after about six weeks' treatment she developed marked exophthalmos, and although the thyroid gland was enlarged to begin with it became very much bigger.

It was decided to use a large dose of glucose so that any variations in the curves would be more evident, and for this reason a comparatively large amount for children (80 grm.) was used. It has been stated that, however large the amount of glucose given, the blood sugar will not rise any higher than if the

CHART OF AVERAGE BLOOD SUGAR CURVES.

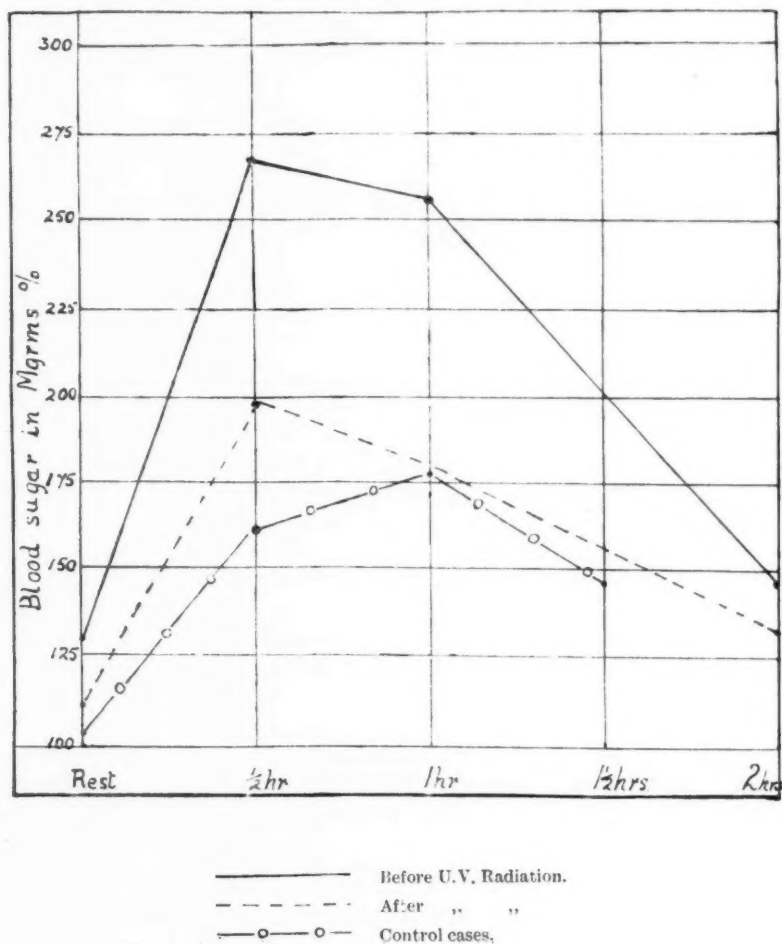


TABLE IV.  
CARBOHYDRATE TOLERANCE AND ULTRA-VIOLET RADIATION RESULTS.

Case No.	Blood sugar : mgrm. per cent.						
	Resting			$\frac{1}{2}$ hour.	1 hour.	$1\frac{1}{2}$ hours.	2 hours.
1	Before	...	145	353	376	—	162
	After	...	118	221	154	—	149
2	Before	...	142	289	317	—	172
	After	...	97	194	146	—	155
3	Before	...	105	238	219	217	—
	After	...	141	210	205	165	84
4	Before	...	141	257	253	—	152
	After	...	139	253	270	—	178
5	Before	...	143	183	148	—	111
	After	...	103	181	155	—	105
6	Before	...	129	327	363	392	—
	After	...	91	220	234	241	156
7	Before	...	124	160	142	—	125
	After	...	70	136	133	—	107
8	Before	...	140	488	442	—	184
	After	...	102	243	189	—	93
9	Before	...	139	218	156	—	114
	After	...	115	175	146	—	114
10	Before	...	110	144	164	142	—
	After	...	125	148	172	166	181
Control 1	...	...	120	149	121	98	—
Control 2	...	...	95	196	168	114	—
Control 3	...	...	99	165	185	156	—
Control 4	...	...	104	152	218	214	—
Control 5	...	...	98	155	219	141	—

maximum dose in grammes per kilogramme of body weight had been used. The particularly high curves obtained in some of the cases gave rise to some doubt whether this dictum was applicable in children. For this reason five control curves were made on normal children about the same age, and as these were found to be within normal limits, it is suggested that these high values were due in most cases to sepsis, or where no obvious focus of pyogenic infection could be discovered, to the original tuberculous disease itself.

The resting sugar was taken at least three hours after a meal and the patients were then given 80 gm. of powdered glucose in water. Blood was taken from a vein at half, one and two-hourly intervals. The proteins were precipitated immediately in almost all cases and the blood sugar estimated by the colorimetric method (Folin and Wu).

#### *Conclusions.*

(1) It would appear that in patients suffering from tuberculous lesions the carbohydrate tolerance is increased following exposures to ultra-violet radiation.

(2) As has been stated no conclusion regarding any association between carbohydrate metabolism, ultra-violet radiation, and the suprarenal capsules can be assumed, because so many other aspects must be taken into consideration. Such an association may, however, be suspected.

### IV. EXPERIMENTAL DATA & CONCLUSIONS.

#### EXPERIMENTAL DATA.

The following charts represent the numerical readings of the tests involved ; but it must be emphasized that the conclusions are based not only on these tests, but also in large part on the clinical picture presented by each case, X-Ray reports, the formation and breaking down of abscesses, temperature range, etc.

In certain cases, also, ultra-violet therapy, and/or endocrine therapy, were stopped for occasional periods and the effect on the patient noted. These and other observations have of necessity been omitted, but have been taken into consideration in forming conclusions. It is to be regretted that a time limit had to be fixed for the duration of the tests, and in consequence certain conclusions are immature.

The following scheme has been drawn up with a view to simplifying the results :—

#### A. *Central Lesions.*

- C.1. Early.
- C.2. Moderately advanced but without sinus formation.
- C.3. Advanced with sinuses.

*B. Peripheral Lesions.*

The term 'central lesion' is used to imply a lesion in one of the major joints, spine, hip or knee.

Under the heading 'peripheral lesion' are included lesions of the smaller joints, ankle, elbow, and wrist, adenitis, skin lesions and peritonitis.

## CONCLUSIONS.

*General Conclusions.*

It will be seen from the cases recorded that following the first month's treatment with ultra-violet radiation, many cases show a fall in the sedimentation rate reading, followed by a rise in the succeeding month. This initial fall has been so frequently noted that for descriptive purposes it has been called 'the negative phase.' It will be further noticed that in other cases which are secondarily infected, or in which an abscess is developing, the succeeding rise is at least delayed. It is thought that the significance of this fall is an increased reaction in the focus of disease.

It is also considered that the severity of this reaction is dependent upon three factors :—(1) The severity and site of the lesion : (2) The degree of mixed infection, if present : and (3) The dosage of ultra-violet radiation.

These three factors together with the reaction to light of the individual may, it is thought, provide a basis upon which this adjuvant method of treatment should be prescribed.

Of these three factors there is only one, namely, radiation, which can be varied at will. It is felt that the method of treatment in vogue at present is too empirical, and that this source of natural energy should be used in prescribed doses according to the reaction which might be expected to occur. It is considered that in general diseases a mild response, or possibly a single 'shock' dose, is more desirable than a continued severe, or moderately severe reaction.

Possibly the nearer natural sunshine is simulated for general diseases, and this can be best done by using carbon-arc lamps with mild carbons, the better the results will be. It is felt that adequate control of dosage could be obtained by observations of temperature, sedimentation rate, and skiagrams.

Subject to consideration of the above-mentioned controlling factors, it is thought that in ultra-violet radiation is to be found an adjuvant method of treatment of considerable value and possibility in cases of tuberculosis in children.

*Special Conclusions.*

*A. Central Lesions.* (1) *Early.* It is to be regretted that the number of cases under this heading is small, but from these and the suspected action of ultra-violet radiation it is thought that in this group radiation is of considerable value. It is considered that small doses are probably best, possibly after three months immobilization, when the resistance of the body is expected to be on the up grade.

(2) *Moderately advanced, but without sinus formation.* The clinical impression gained from cases in this group is that there has been a better response to treatment in cases receiving radiation than in corresponding cases in hospital. The sedimentation rates in this section, it is thought, have not been taken over a sufficiently long period in some cases, for where abscesses are present it is to be expected that until they heal completely the sedimentation rate will remain low.

In this group again it is considered there is scope for ultra-violet radiation, but only where the dose is graduated according to the principles laid down in the introduction to this section. Here again the influence of possible secondary infection, although the skin is unbroken, is felt to be of moment.

(3) *Advanced, with sinuses.* With but one exception the results in this group have been disappointing. In the majority that the activity of the disease has been increased to a considerable extent after irradiation is shown by lower sedimentation-rate readings, lower blood pressure, wasting, increased discharge from sinuses, and in three cases by death. It is considered that ultra-violet radiation accelerated this result.

It would appear that in the presence of a large focus of pyogenic infection, radiation either lowers the bodily resistance or activates the bacteria to a much greater extent than the resistance of the body can withstand.

Although the results obtained in this group have been poor it must be remembered that the dosage in all cases was empirical and that no change was made from the routine. It is possible that if this dose could be controlled and this type of case receive a much shorter exposure, by coaxing the resistance of the body some benefit might be obtained.

B. *Peripheral Lesions.* The treatment of peripheral lesions by ultra-violet radiation is the most favourable field for this mode of therapy.

*Disease of the ankle and elbow joints,* with or without sinuses do well, and also tuberculous *skin lesions.* It is of interest to note that the sinuses of peripheral lesions heal more rapidly with radiation than without.

*Cases of tuberculous peritonitis,* diagnosed clinically or with physical signs, improve immensely, except those which are advanced. There is also a feeling that the stay in hospital of these cases is shortened.

*Glands of neck.* It was noticed that following a few exposures to radiation in a number of cases of cervical adenitis the glands broke down, with extrusion of their contents through the skin, but that in others, after first becoming further enlarged and rather tender, they retracted and became extremely hard. It is thought that the condition of the glands as regards softening at the commencement of treatment, and particularly the influence of local sepsis, teeth, tonsils, etc., play some part in the reaction of the glands to radiation. Great care is required in treating cases of cervical adenitis, and the dose must be carefully regulated. Where there is a sinus present good results were almost always obtained.

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